PUBLISHED MONTHLY

VOLUME XXXVI • NUMBER 2
AUGUST 1959

DISEASES of the CHEST

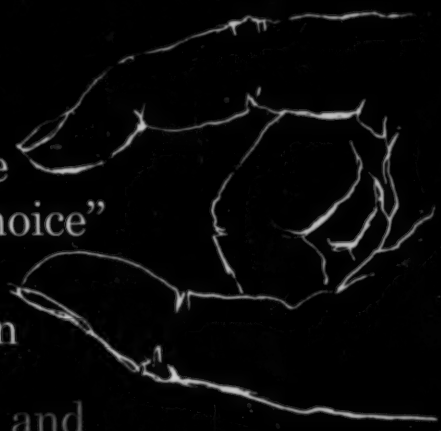
OFFICIAL PUBLICATION

Silver Anniversary Year

PROGRAM ISSUE
Homecoming Meeting
Albuquerque, New Mexico, October 14-17, 1959

Interim Session
Dallas, Texas, November 29-30, 1959

right from the start!



the "right choice" antibiotic for use in

- skin, soft tissue and post-surgical infections
- genito-urinary infections
- respiratory tract infections

due to staph or "gram-negatives"

KANTREX

KANAMYCIN SULFATE INJECTION

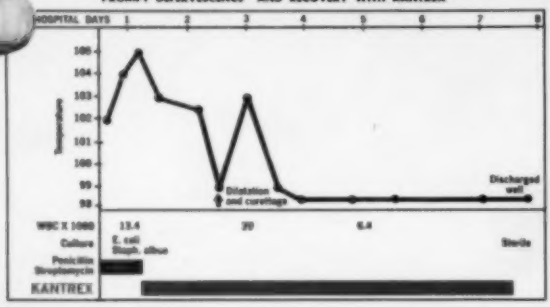
INJECTION

- rapidly *bactericidal* – not merely bacteriostatic
- minimizes emergence of bacterial resistance
- clinically safe in specified dosage
- effective against many organisms resistant to other antibiotics

For prompt therapeutic results, KANTREX is the "right choice" antibiotic to use in infections due to staph or gram-negatives.

POSTABORTAL SEPSIS

"PROMPT DEFERVESCENCE" AND RECOVERY WITH KANTREX



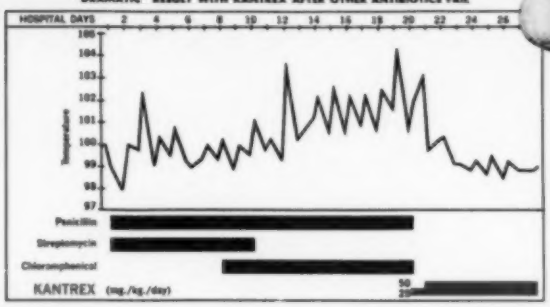
. . . in genito-urinary infections
(due to staph or "gram-negatives")

N. A., a 27-year-old female with post-"ortal sepsis due to *E. coli* and *Staph. albus* had "prompt defervescence" and recovery with KANTREX after 2 other antibiotics had proved ineffective. No toxic effects were observed.

—Rutenburg, A. M., Keats, G. M., and Schwesinger, F. B.: Annals N.Y. Acad. Sci. 76:340, 1958.

APPENDICEAL ABSCESS

"DRAMATIC" RESULT WITH KANTREX AFTER OTHER ANTIBIOTICS FAIL



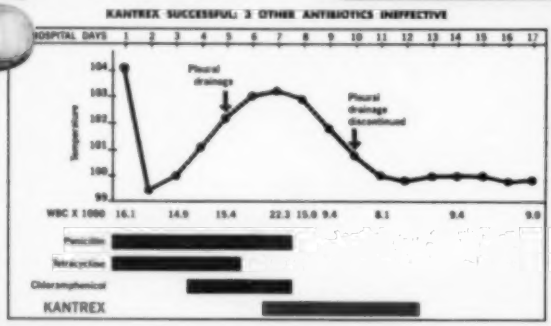
. . . in skin, soft tissue and post-surgical infections
(due to staph or "gram-negatives")

J. H. W., 12-year-old boy with appendiceal abscess due to *Staph. aureus*, showed a "clear-cut" and "dramatic" response to KANTREX after 3 other antibiotics had failed. No toxic reactions were noted.

—Yow, E. M., and Mooney, O. T.: Annals N.Y. Acad. Sci. 76:372, 1958.

STAPH PNEUMONIA

KANTREX SUCCESSFUL: 3 OTHER ANTIBIOTICS INEFFECTIVE



. . . in respiratory tract infections
(due to staph or "gram-negatives")

T. A., a 4-week-old female infant with pneumonia, pyoderma and septicemia due to *Staph. aureus* showed a prompt beneficial effect and uneventful recovery with KANTREX after 3 other antibiotics had proved unsuccessful. "No serious untoward reactions were observed."

—Riley, H. D., Jr.: Antibiotics Annual 1956-1957, p. 628

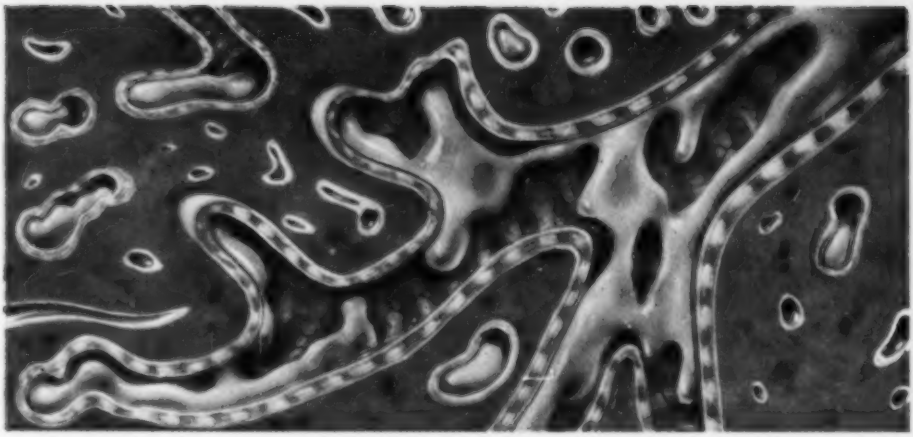
KANTREX INJECTION

KANAMYCIN SULFATE INJECTION

Bristol

BRISTOL LABORATORIES INC., Syracuse, New York

KANTREX sensitivity discs and comprehensive literature available on request.



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PANCREATIC DORNASE

- DORNAVAC starts on contact to reduce tenacity and viscosity of mucopurulent bronchial secretions.
- DORNAVAC specifically lyses desoxyribonucleoprotein, which constitutes 30 to 70 per cent of purulent bronchial exudates. Striking clinical improvement often begins within 30 minutes after aerosol therapy.
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Indications: purulent bronchitis, bronchiectasis, atelectasis, emphysema, unresolved pneumonia and chronic bronchial asthma.

Supplied: Each combination package contains one vial of lyophilized pancreatic dornase (100,000 units) and one 2 cc. vial of sterile diluent.

for inhalation therapy in bronchopulmonary disease

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Division of Merck & Co., Inc.
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Additional information is available to physicians on request. Address Professional Service Department, West Point, Pa.

VOLUME XXXVI AUGUST, 1959 NUMBER 2

CONTENTS

SECTION ON CARDIOVASCULAR DISEASES

CASE REPORT SECTION

Second Class Postage Paid at Chicago, Illinois

Annual Subscription: $15.00, postpaid to any part of the world

THE HEART DISEASE PATIENT NEEDS RELIEF FROM EMOTIONAL STRESS

ANXIETY INTENSIFIES the physical disorder in heart disease. "The prognosis depends largely on the ability of the physician to control the anxiety factor, as well as the somatic disease."
(Friedlander, H. S.: The role of ataraxics in cardiology. Am. J. Cardiol. 1:395, March 1958.)

TRANQUILIZATION WITH MILTOWN enhances recovery from acute cardiac episodes and makes patients more amenable to necessary limitations of activities.
(Waldman, S. and Pelner, L.: Management of anxiety associated with heart disease. Am. Pract. & Digest Treat. 8:1075, July 1957.)

Miltown®

meprobamate (Wallace)

Available in 400 mg. scored and 200 mg. sugar-coated tablets. Also available as MEPROSPAN® (200 mg. meprobamate *continuous release* capsules). In combination with a nitrate, for angina pectoris: MILTRATE®—(Miltown 200 mg. + PETN 10 mg.). ®TRADE-MARK CM-7705

Miltown causes no adverse effects on heart rate, blood pressure, respiration or other autonomic functions.

WALLACE LABORATORIES, *New Brunswick, N. J.*

DISEASES *of the* CHEST

OFFICIAL PUBLICATION

OF THE

AMERICAN COLLEGE OF CHEST PHYSICIANS

EXECUTIVE OFFICE

112 East Chestnut Street, Chicago 11, Illinois, U.S.A.

MURRAY KORNFELD, *Managing Editor*

WARD BENTLEY, *Publication Manager*

CALENDAR OF EVENTS

National Meetings

Homecoming Meeting

Silver Anniversary,
American College of Chest Physicians
Albuquerque, New Mexico,
October 14-17, 1959

Interim Session

American College of Chest Physicians
Dallas, Texas, November 29-30, 1959

Postgraduate Courses

14th Annual Course, "Clinical Cardiopulmonary Physiology"
Chicago, Illinois, October 5-9, 1959

12th Annual Course on Diseases of the Chest
New York City, November 9-13, 1959

5th Annual Course on Diseases of the Chest
Los Angeles, December 7-11, 1959

Chapter Meetings

Kentucky Chapter,
Louisville, September 23

Virginia Chapter, Roanoke, October 4

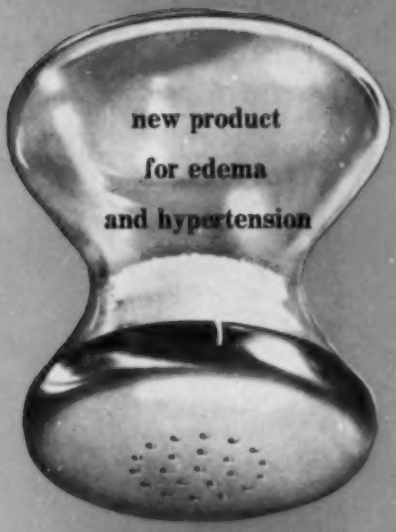
Indiana Chapter, Indianapolis,
October 7

Potomac Chapter,
White Sulphur Springs,
West Virginia, October 9

Colorado Chapter, Denver,
October 30-31

Southern Chapter, Atlanta,
November 15-16


Doctor:
if you have low-salt patients
you can
put some real pleasure
(and some real salt)
back on their table
...take rigid diet plans
(and all their bother)
out of your treatment



your most potent means when the end is saluresis*

ORETIC™

(HYDROCHLOROTHIAZIDE, ABBOTT)

In simplest terms, giving new **ORETIC** is like packaging a low-salt regimen in a single tablet . . . because **ORETIC** steps up excretion of sodium and chloride, and thereby often cuts down the need for an extremely rigid diet.

Further, it makes sense that the more potent the diuretic-antihypertensive, the greater the chances that sodium restrictions can be relaxed.

And new **ORETIC** is the most potent, most effective oral diuretic-antihypertensive yet discovered. It has a high therapeutic ratio, low toxicity. It works successfully with dosages only 1/10—1/15 those of chlorothiazide.

If you have low-salt patients . . . patients with hypertension, renal edema, congestive heart failure, toxemia of pregnancy . . . consider **ORETIC**. Because if you adjust **ORETIC** dosage and sodium intake together, you may well find that you can put some real pleasure (and some real salt) back on the patient's table . . . and spend a lot less time and effort attending to details of rigid diet-planning.

New **ORETIC** is available for your trial in 25- and 50-mg. tablets, bottles of 100 and 1000.

Ask your Abbott representative for a copy of the **ORETIC** PHYSICIAN'S LITERATURE *containing* complete *indications, dosage and precautionary information.*

ABBOTT

*In many clinical problems the elimination of salt (saluresis) is just as important as diuresis. And Oretic provides your most potent means to these ends.

ORETIC | YOUR MOST POTENT MEANS WHEN THE END IS SALURESIS*

ORETIC—TRADEMARK FOR HYDROCHLOROTHIAZIDE, ABBOTT

RELIEVES ANXIETY IN HYPERTENSIVE PATIENTS *without producing depression*

Miltown relieves mental pressure which often aggravates symptoms of hypertension and impairs effectiveness of antihypertensive therapy.

Combined with specific therapy, Miltown provided greater over-all improvement in hypertensive patients than antihypertensive therapy alone.[1,2] In 58 patients receiving combined therapy, over 90% (including moderate and severe cases) benefited from relief of headache, nervousness, palpitations, insomnia, weakness and dizziness.[1,2]

Miltown was found "a useful adjunct in the treatment of the psychogenic and neurogenic components of hypertension."[3]

Miltown®
meprobamate (Wallace)

- does not cause depression
- does not interfere with heart rate, blood pressure, respiration, G.I. function or other autonomic mechanisms

1. Nussbaum, H. E., Leff, W. A., Mattia, V. D., Jr. and Hillman, E.: Am. J. M. Sc. *234*:150, Aug. 1957. 2. Dunsmore, R. A., Dunsmore, L. D., Bickford, A. F. and Goldman, A.: Am. J. M. Sc. *233*:280, March 1957. 3. Boyd, L. J., Huppert, V. F., Mulinos, M. G. and Hammer, H.: Am. J. Cardiol. *3*:229, Feb. 1959.

SUPPLIED: 400 mg. scored and 200 mg. sugar-coated tablets in bottles of 50. Also available as MEPROSPAN® (Miltown *continuous release* capsules). ®TRADE-MARK

Literature and samples on request.

CH-9204

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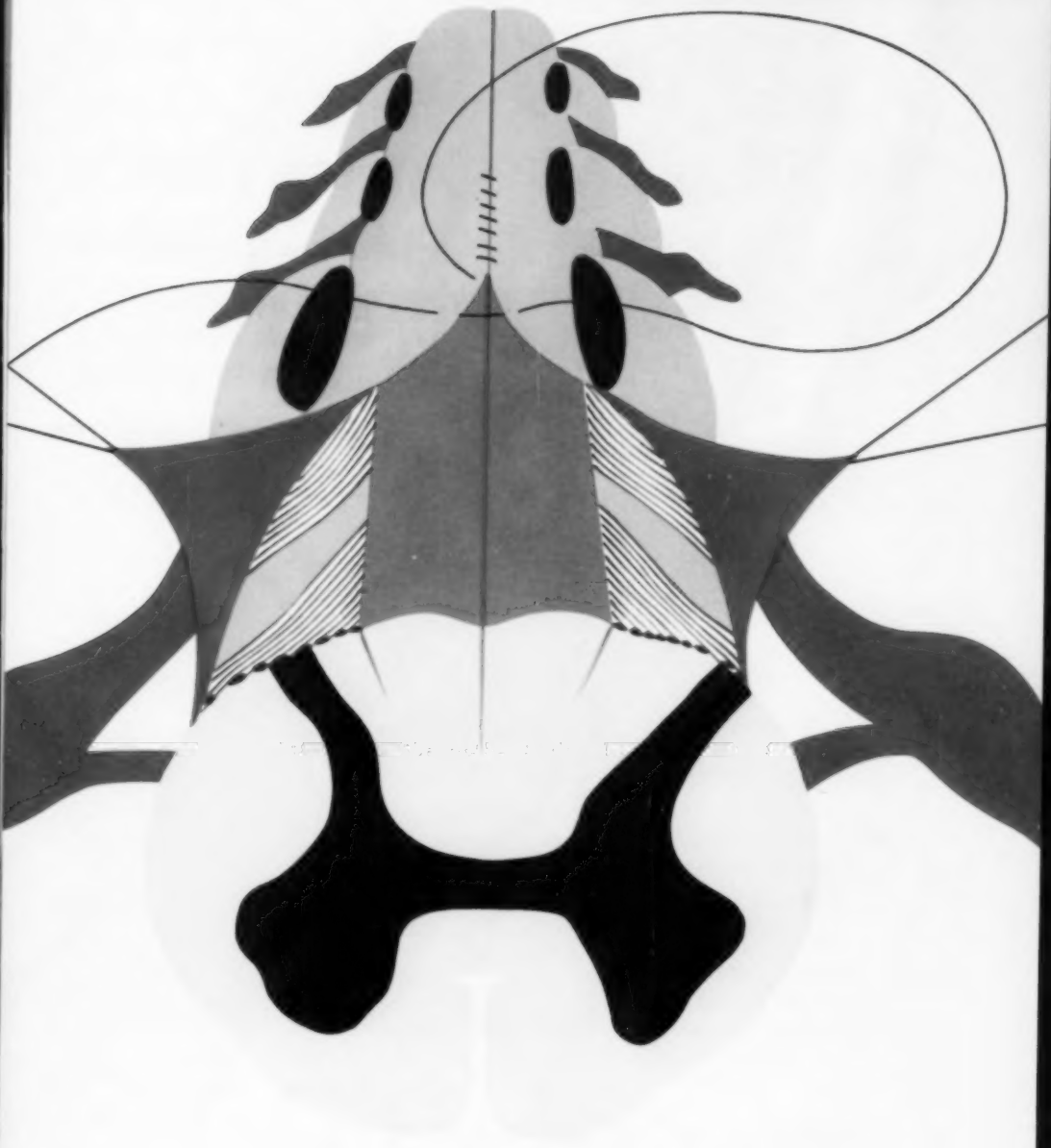

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In Coronary Insufficiency...

Your high-strung angina patient often expends a "100-yd. dash" worth of cardiac reserve through needless excitement.

Curbs emotion as it boosts coronary blood supply

CONTROL OF EMOTIONAL EXERTION with Miltrate leaves him more freedom for physical activity.

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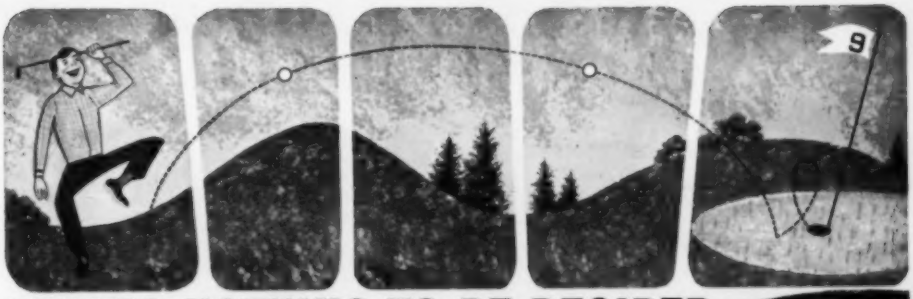
Miltown® (*meprobamate*) + PETN

Each tablet contains: 200 mg. Miltown and 10 mg. pentaerythritol tetranitrate.
Supplied: Bottles of 50 tablets.
Usual dosage: 1 or 2 tablets q.i.d. *before meals* and at bedtime. Dosage should be individualized.

WALLACE LABORATORIES · *New Brunswick, N. J.*

CML-9159-59 *TRADE-MARK



LEAVES NOTHING TO BE DESIRED

HYCOMINE® Syrup

THE COMPLETE Rx FOR COUGH CONTROL

cough sedative / antihistamine / expectorant

- relieves cough and related symptoms in 15-20 minutes
- effective for 6 hours or longer • promotes expectoration
- rarely constipates • cherry-flavored

Each teaspoonful (5 cc.) contains:

Hycodan®		
Dihydrocodeinone Bitartrate	5 mg.	6.5 mg.
(Warning: May be habit-forming) Homatropine Methylbromide	1.5 mg.	
Pyrilamine Maleate		12.5 mg.
Ammonium Chloride		60 mg.
Sodium Citrate		85 mg.

Supplied: as a pleasant-to-take syrup. May be habit-forming.
Federal law permits oral prescription.

Endo

Literature on request

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Richmond Hill 18, New York

UNUSUALLY EFFECTIVE IN RELIEVING ANXIETY IN APATHETIC, EMOTIONALLY FATIGUED PATIENTS

'Stelazine' is a new long-acting psychotherapeutic agent that can help you to bring prompt relief to many of your patients whose anxiety is expressed as apathy, listlessness and emotional fatigue.

Clinical studies in over 12,000 patients have shown that 'Stelazine' is outstanding among agents in its class because it not only relieves agitation and tension, but also *restores normal drive* in many patients who are apathetic due to anxiety.

These studies have also shown that 'Stelazine' is effective in low b.i.d. dosage (2 to 4 mg. daily) and that it is often effective in patients who have failed to respond to meprobamate, prochlorperazine, phenobarbital, mepazine, chlorpromazine, or promazine.

RECOVERY OF NORMAL DRIVE IN APATHETIC PATIENTS

Clinicians report that with 'Stelazine' most apathetic, listless and emotionally fatigued patients regain an alert, more confident outlook. This frequently results in increased mental and physical activity. For example:

> Patients' "spirits brightened and initiative and interest picked up considerably in contrast to their pretreatment inertia."[1]
>
> 'Stelazine' "seemed to have a capacity to restore normal drive in conditions characterized by decreased motor activity and mental apathy."[2]

ADDITIONAL INFORMATION will reach you by mail or through your S.K.F. representative. We hope you'll decide that 'Stelazine' deserves an early trial. Smith Kline & French Laboratories, Philadelphia.

REFERENCES: 1. Gearren, J.B.: Dis. Nerv. System *20*:66 (Feb.) 1959. 2. Margolis, E.J., et al.: Scientific Exhibit at 12th Clinical Meeting of the American Medical Association, Minneapolis, Dec. 2-5, 1958. 3. Phillips, F.J., and Shoemaker, D.M.: *ibid.* 4. Ayd, F.J., Jr.: Clin. Med. 6:387 (Mar.) 1959. 5. Tedeschi, D.H., et al.: in *Trifluoperazine: Clinical and Pharmacological Aspects*, Philadelphia, Lea & Febiger, 1958, pp. 23-33.

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We spent six years developing and hospital-testing this heated aerosol idea. Now it's perfected and being offered to hospitals for IPPB therapy. We call it "Mainstream Tepid Mist" nebulization. Now a patient's entire air stream can be humified... continuously. And because the air (or gas) is warmed to body temperature, these benefits occur:

Is more comfortable for the patient, more penetrating and carries solution reagents to the site of mucous plugging and infection.

Warm air carries more moisture.

Eliminates the generally associated desiccation of the bronchial mucosa.

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Administration Office

Joseph K. Dennis Company, Inc.
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175 W. Jackson Boulevard Chicago 4, Illinois

DO NOT SEND MONEY
WITH YOUR APPLICATION . . .
YOU WILL BE INVOICED

YOUR BENEFITS . . .

This table illustrates the amount of insurance in force at various ages. (Example: If death occurs at Age 40, the Insured's Beneficiary would receive $13,410.00.)

ATTAINED AGE	NATURAL DEATH BENEFITS	ACCIDENTAL DEATH & DISMEMBERMENT
25	$20,000	$40,000
26	20,000	40,000
27	20,000	36,000
28	20,000	33,000
29	20,000	30,000
30	20,000	27,000
31	20,000	24,000
32	20,000	22,000
33	20,000	
34	19,064	
35	18,068	
36	17,042	
37	16,096	
38	15,174	
39	14,260	
40	13,410	
41	12,586	
42	11,794	
43	11,040	
44	10,320	
45	9,634	
46	8,990	
47	8,372	
48	7,798	
49	7,246	
50	6,736	
51	6,254	
52	5,802	
53	5,378	
54	4,982	
55	4,614	
56	4,272	
57	3,952	
58	3,656	
59	3,378	
60	3,122	
61	2,844	
62	2,662	
63	2,460	
64	2,270	
65	2,094	
66	1,932	
67	1,784	
68	1,644	
69	1,518	
70	1,400	

AMERICAN COLLEGE OF CHEST PHYSICIANS APPLICATION to the Massachusetts Mutual Life Insurance COMPANY for Term Life Insurance (decreasing) to Age 70. Please print or type all information.

Name _____ (Last) _____ (First) _____ (Middle Initial)

Address _____ (Street) _____ (City) _____ (Zone) _____ (State)

Present Height _____ Weight _____ Date of Birth _____ (Month) _____ (Day) _____ (Year)

Beneficiary _____ Relationship _____

Do you know of any existing impairment in your health or physical condition?

No_____ Yes_____ If Yes—Give Particulars _____

Have you consulted a physician for any illness during the past five years?

No_____ Yes_____ If Yes—Give Particulars _____

I hereby apply for this insurance and agree to pay the annual deposit as specified ($100.00 annually) for the first year and thereafter.
INFORMATION in this application is true and complete to the best of my knowledge and belief. The Company shall incur no obligation because of this application unless and until a Certificate is delivered to the Applicant and the first deposit is made in full while the health or other conditions affecting insurability of the Applicant are as described in this application.

_____, 19____ _____
Date Signature of Applicant

Hotel Reservation Form
HOMECOMING MEETING
AMERICAN COLLEGE OF CHEST PHYSICIANS
Albuquerque, New Mexico
October 14-17, 1959

Reservations
Western Skies Hotel
13400 Central, S.E.
Albuquerque, New Mexico

Name .....

Address .....

City..... State.....

Arrival Date..... Departure Date.....

Please Reserve Room Indicated By X

Cabana and Patio: Pool Side

	Single	Double
Double	.....10.50	.....13.00
Twin	.....11.50	.....15.00
Studio	.....12.00	.....16.00

Patio Scenic Side

	Single	Double
Double	..... 9.50	.....12.00
Twin	.....10.50	.....14.00
Studio	.....11.00	.....15.00

West and Main

	Single	Double
Double	..... 8.50	.....11.00
Twin	..... 9.50	.....14.00
Studio	.....10.00	.....14.00

Main and Scenic

	Single	Double
Double	..... 8.00	.....10.00
Twin	..... 8.50	.....12.00
Studio	..... 9.00	.....13.00

Family Accommodations:.....How Many?.....Adults.....Children

If rate requested is not available, next higher rate will be assigned. In event accommodations are not available at the Western Skies, a reservation will be made for you at a nearby motel, which will confirm this reservation directly to you.

KENACORT

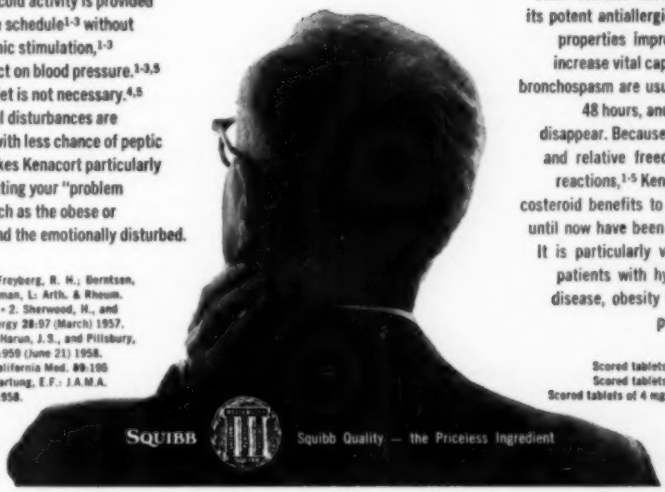
SQUIBB TRIAMCINOLONE

for all your patients starting on corticoids

Kenacort safely starts your patients off right — with all the benefits of systemic corticosteroid therapy and few side effects to worry about. Increased corticoid activity is provided on a low dosage schedule[1-3] without edema,[1-4] psychic stimulation,[1-3] or adverse effect on blood pressure.[1-3,5] A low sodium diet is not necessary.[4,5] Gastrointestinal disturbances are negligible[2,4,5] with less chance of peptic ulcer.[4] This makes Kenacort particularly valuable in treating your "problem patients" — such as the obese or hypertensive and the emotionally disturbed.

for all your allergic patients requiring corticoids

Kenacort, in treating your allergic patients, has proved effective where other steroids have failed. In asthma, its potent antiallergic and inflammatory properties improve ventilation and increase vital capacity.[2] Dyspnea and bronchospasm are usually relieved within 48 hours, and sibilant râles often disappear. Because of its low dosage[1-3] and relative freedom from untoward reactions,[1-5] Kenacort provides corticosteroid benefits to many patients who until now have been difficult to control. It is particularly valuable for allergic patients with hypertension, cardiac disease, obesity and those prone to psychic disturbances.



REFERENCES: • 1. Freyberg, R. H.; Bernstein, C. A., Jr., and Heilman, L.: Arth. & Rheum. 1:215 (June) 1958. • 2. Sherwood, H., and Cooke, R. A.: J. Allergy 28:97 (March) 1957. • 3. Shelley, W. B.; Harun, J. S., and Pillsbury, D. M.: J.A.M.A. 167:959 (June 21) 1958. • 4. Dubois, E.L.: California Med. 89:195 (Sept.) 1958. • 5. Hartung, E.F.: J.A.M.A. 167:973 (June 21) 1958.

SUPPLIED:
Scored tablets of 1 mg. — Bottles of 50
Scored tablets of 2 mg. — Bottles of 50
Scored tablets of 4 mg. — Bottles of 30 and 100

SQUIBB Squibb Quality — the Priceless Ingredient

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Six-year medical center trained thoracic surgeon desires group or solo practice with cardiovascular emphasis. Please address inquiries to Box 305B, American College of Chest Physicians, 112 East Chestnut Street, Chicago 11, Illinois.

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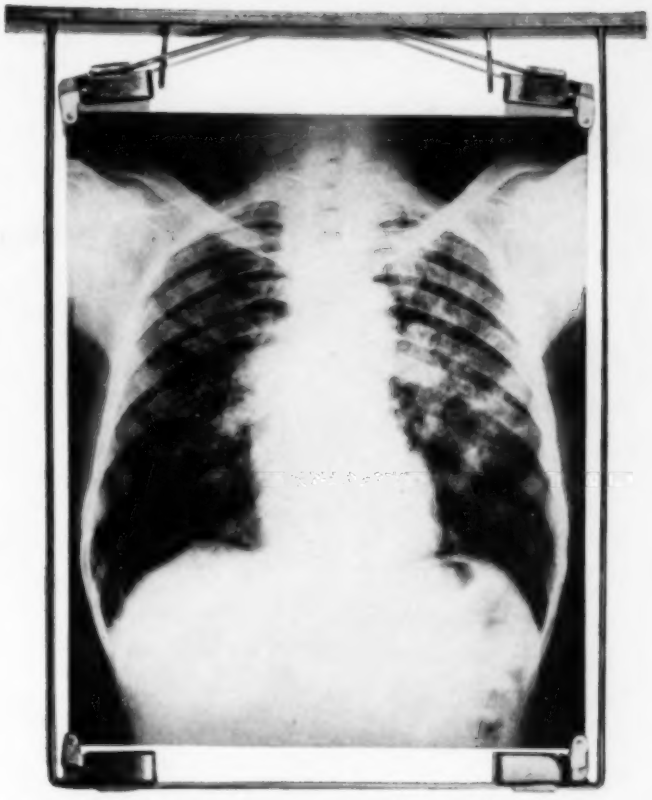
For Illinois mental hospitals, schools and institutions: career vacancies exist in the following: tuberculosis control physicians—annual salaries $8,496 to $20,040; retirement; Illinois licensure. Liberal annual leave, 11 paid holidays, excellent pension plan, nominal deduction for maintenance, allowance for board certification, Civil Service below superintendent. For further information, please contact: Paul Hletko, M.D., Chief Medical Officer, Illinois Department of Public Welfare, 160 North LaSalle Street, Chicago, Illinois, FInancial 6-2000.



when tuberculosis defies routine therapy

VIOCIN®

brand of
viomycin sulfate

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In at least half the cases of tuberculosis that might otherwise have been said to have "no prognosis," Viocin® (viomycin sulfate) has been used with success, in stabilizing and even arresting resistant progressive disease.[1-2] Toxicity observed with viomycin is related chiefly to dosage. When recommended dosages and precautions are followed, toxic reactions are unlikely to occur with any degree of frequency or severity. Consult professional literature for details of dosage, administration, contraindications and toxicity.

Also available for tuberculosis therapy:

streptomycin sulfate—dry powder and solution • *dihydrostreptomycin sulfate*—dry powder and solution • *Streptohydrazid**—a crystalline compound combining streptomycin and isoniazid • *Cotinazin*®—brand of isoniazid • *Combistrep**—brand of streptoduocin—equal parts of streptomycin and dihydrostreptomycin.

References: 1. McLean, R. L., and Benson, W. P.: Tr. 15th Conference on Chemotherapy of Tuberculosis, 1956, p. 122. 2. Murdoch, J. M., and Stewart, S. M.: Brit. J. Tuberc. 50:85 (Jan.) 1956.

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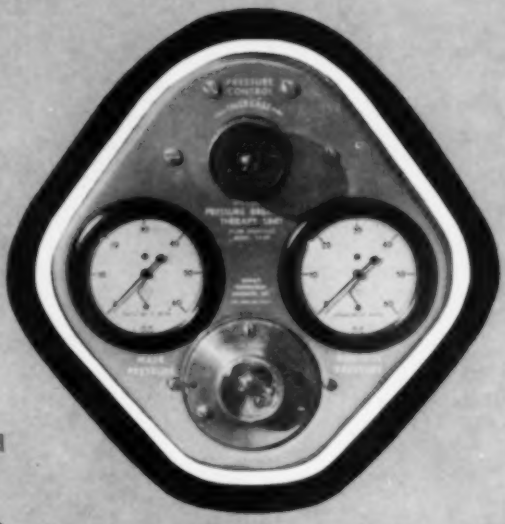
TV-2P

The most widely used and accepted unit for IPPB therapy in hospital, office or home, Bennett Model TV-2P has been designed to provide safe, effective breathing assistance . . . completely patient-controlled because of the unique features of the *flow-sensitive* Bennett Valve.



Adaptations of this famous basic unit are illustrated below. We invite you to write for literature and reprints or demonstration.

Model PV-3P
Pedestal-mounted for use with piped oxygen systems

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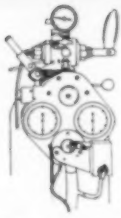

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DISEASES of the CHEST

VOLUME XXXVI AUGUST, 1959 NUMBER 2

Mesotheliomas of the Pleura

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The purpose of this paper is to report our experience with a series of mesotheliomas of the pleura seen and treated between 1948 and 1956.† Clinical data of diagnostic value will be presented.

Mesotheliomas are controversial tumors. In general three concepts of origin are in vogue. The first is expressed by Robertson[1] who feels that there is no tumor of mesothelial origin and that all tumors so diagnosed are in reality metastatic carcinoma primary in the lung.

The second concept was proposed by Klemper and Rabin,[2] who divide these tumors into solitary pleural tumors, both benign and malignant, and a diffuse one which is always malignant. These authors feel that the solitary tumors are mesenchymal in origin and arise from the sub-pleural tissues. The localized type usually has the structure of a cellular fibroma or a fibrosarcoma. The diffuse tumor, which is believed to be mesothelial in origin arising from the lining cells of the pleura, is usually epithelial in appearance, but may contain sarcomatous elements or even occasionally a pure sarcomatous pattern. Yezner and Herwitz[3] report a solitary mesothelial tumor whose cellular elements were distinctly epithelial in character while Sano et al., reported a diffuse tumor, the predominant cell type being sarcomatous. There are then exceptions to the usual rule that solitary tumors are fibromatous in appearance and the diffuse tumor epithelial.

The third concept regarding these tumors is proposed by Stout and Murray.[5] In 1942, by tissue culture technique, they confirmed and expanded the work of Maximow,[6] who had shown that explanted normal mesothelial tissue could and does assume characteristics of fibrous tissue. Stout and Murray's solitary visceral pleural tumor whose cell type was that of a fibrosarcoma, on tissue culture, grew out as "epithelial cells"

The statements and conclusions published by the authors are the result of their own study and do not necessarily reflect the opinion or policy of the Veterans Administration.

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TABLE I—MESOTHELIOMAS OF THE PLEURA

	Benign	Malignant
Diffuse		6
Solitary	1	1

characteristic of a diffuse mesothelioma. This would seem to imply that both the solitary and diffuse types are mesothelial in origin. Sano et al.,[4] using tissue from a diffuse mesothelial tumor predominantly spindle cell in type, were able to show in tissue culture that these cells assume "epithelial" characteristics of a type usually found in the diffuse mesothelial tumor.

Embrologically, the lining of the pleura and peritoneal cavities develop from celomic epithelium, which in turn, arises from the mesoderm. The subpleura tissues arise from the mesenchyme, which itself arises originally from the mesoderm. This would suggest at least, that while the diffuse tumor and the solitary tumor are usually quite different in cellular characteristics and in behavior, they have a common origin in the mesoderm.

Material

Using the classification of Stout and Murray,[5] our series consist of two solitary and six diffuse neoplasms (Table I). The two solitary tumors are divided equally between benign and malignant types. A brief history of the cases follows.

Diffuse Mesotheliomas

Case 1: F. F. M., a 51 year old white man was admitted to the Veterans Administration Hospital, Augusta, Georgia, October, 1955, with the history of progressive weakness and dyspnea since November, 1954. Left pleural effusion was first noted in February, 1955. Several thoracenteses in other hospitals yielded bloody fluid. Exploratory thoracotomy and partial decortication in this hospital in October, 1955 revealed diffuse involvement of all pleural and pericardial surfaces by dense fibrous tissue. Complete study of the gastrointestinal, genito-urinary and pulmonary tracts had failed to reveal any other primary site. Treatment consisted of four courses of

FIGURE 1

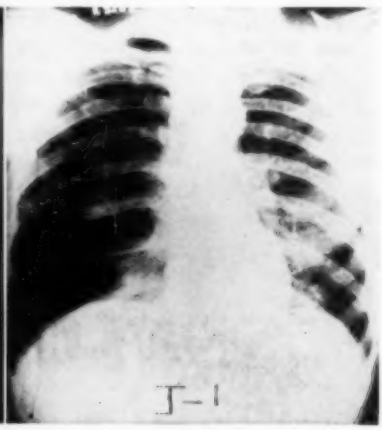

FIGURE 2

Figure 1 (Case 2): X-ray film July 26, 1956, one month from onset, showing massive left effusion (hemorrhagic).—*Figure 2* (Case 3): X-ray film January 8, 1952. Three years prior to onset. Note partial right pneumothorax.

nitrogen mustard plus ACTH over the next six months. He showed slow weight loss, progressive weakness, and moderate chest pain. He died at home in June, 1956 from coronary thrombosis. Sections of the pleura showed neoplasm which presents the frequent differential diagnostic problem of metastatic carcinoma versus pleural mesothelioma. On the basis of information and material available the case is quoted as either a diffuse mesothelioma or an anaplastic adenocarcinoma.

Case 2: C. L. S., a 32 year old white man, was admitted on July 17, 1956. Sudden onset left chest pain began June 20, 1956. X-ray film at that time was entirely negative. Chest pain persisted and weakness and dyspnea rapidly developed over the next nine days. X-ray film on June 29, 1956 showed nodulation over the peripheral left lung field, especially over the apex of the lung and lateral thoracic wall. At the time of admission here an x-ray film (Fig. 1) showed massive left pleural effusion, and he was having marked dyspnea. Repeated thoracenteses of bloody fluid were done. Careful study of the gastrointestinal, genito-urinary and respiratory tracts failed to reveal any primary tumor site. Exploratory thoracotomy on July 31, 1956 revealed the parietal and visceral pleura over the chest wall and lung, pericardium and diaphragm, to be studded with a thick nodular tumor. Treatment consisted of two courses of nitrogen mustard plus ACTH given over the next six weeks. There was rapid increase of fluid and metastases to the thoracotomy scar. Severe dyspnea, anorexia, and weight loss ensued. He died at home on September 2, 1956. The dense fibrous tissue on one pleural surface revealed atypical cells having a moderate amount of pale, eosinophilic cytoplasm and large irregular hyperchromatic nuclei. These cells were generally in sheets but occasionally exhibited spaces formed by fine reticular prostheses of the cytoplasm. Diagnosis: Diffuse mesothelioma, left pleural cavity.

Case 3: A. J., a 41 year old colored man became ill with shortness of breath and pain in the right chest in December, 1954. He gave a past history of three episodes of right spontaneous pneumothorax over the preceding two years (Fig. 2). He was admitted to the hospital, January 7, 1955 with marked dyspnea, fever, weakness, and massive right pleural effusion (Fig. 3). Thoracentesis of 2500 cc. of sanguinous fluid was done, rapid recurrence necessitated closed thoracotomy on January 8, 1955. Because of continued slow bleeding, exploratory thoracotomy was carried out January 9, 1955. Findings were that of a diffuse tumor involving the visceral and parietal pleura, pericardium and diaphragmatic pleura. This was both extremely fibrous and also in places quite friable and vascular. Postoperatively, he rapidly deteriorated over the next few days and died on January 27, 1955. Autopsy failed to reveal any other primary site. Mediastinal lymph nodes were involved with the same tumor as the pleura. The nodules showed dense masses of small cells having deep eosinophilic cytoplasm and relatively large hyperchromatic nuclei. In general, the nuclei were eccentrically placed. In most instances the cells appeared to rest upon a thin strand-like fibular network. Many of the cells presented irregular or multiple nuclei. In many instances, the cells were arranged in rows and in others appeared to lie in ill defined spaces. There was moderate to marked amount of

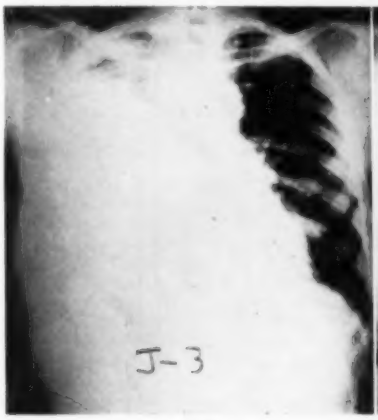

FIGURE 3

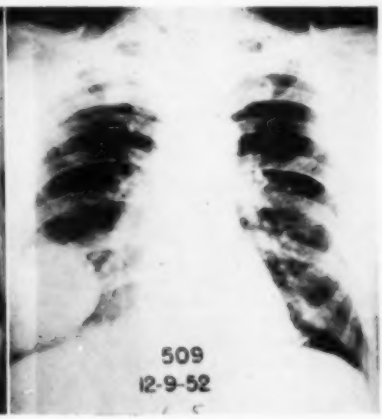

FIGURE 4

Figure 3 (Case 3): X-ray film January 5, 1955, three weeks after onset of symptoms, showing massive right effusion (hemorrhagic). (X-ray film November 21, 1954, was entirely negative except for some blebs in right upper lobe.)—*Figure 4* (Case 1, Solitary Mesothelioma): X-ray film December 9, 1952, showing 10 cm. nodule, right lower lung field with no effusion.

TABLE II

MESOTHELIOMAS OF THE PLEURA: CLINICAL DATA

Patient	Age	Sex	Chest Pain	Joint Pain	Cough	Dyspnea	Prior Pul. Disease	Duration Symptoms	Effusion	Results
Diffuse										
F. S. M.	51	M	+	—	+	+	—	3 Mo.	Bloody	Death 19 Mo.
C. S.	32	M	+	—	+	+	—	1 Wk.	Bloody	Death 3 Mo.
A. J.	41	M	+	—	—	+	Pnx.	1 Mo.	Bloody	Death 2 Mo.
J. H. Y.	56	M	+	—	—	+	—	3 Mo.	Bloody	Death 40 Mo.
J. D. McK.	32	M	+	—	—	+	—	2 Wks.	Bloody	Death 14 Mo.
P. B. L.	24	M	+	—	—	+	Pnx.	1 Wk.	Bloody	Death 6 Mo.
Solitary										
F. H. L.	59	M	—	—	—	—	0	—	0	Living 4 yrs.
H. T. DeB.	58	M	—	—	—	—	0	—	0	Living 1 yr.

connective tissue proliferation associated with these atypical cells. There was slight lymphocytic infiltration in some zones. Diagnosis: Diffuse mesothelioma.

Case 4: J. H. Y., a 56 year old white man developed symptoms of fatigue, slight weight loss and indigestion in September 1949. Ascites first developed in December 1949. Following paracentesis he was apparently much improved until the fall of 1950 when recurrent ascites was noted. From November 1950 until time of admission in January 1952, paracentesis was required every five to six weeks. Pleural effusion on the right was first detected October 1951 but he had noted dyspnea several months prior. On admission, January 15, 1952, he was found to have massive hemorrhagic right pleural effusion, ascites, and a large firm mass in the lower abdominal wall at the site of previous paracentesis. Biopsy was interpreted as "metastatic carcinoma." Gastrointestinal series, barium enema and genito-urinary tract studies were negative. He declined slowly and was finally permitted to go home on November 20, 1952, but returned February 10, 1953, in extremis with marked dyspnea, increase in the right pleural effusion, moderate left pleural effusion and marked ascites. He expired on April 25, 1953. Autopsy revealed involvement of the right and left pleural cavities by dense tumor tissue. The peritoneal cavity was involved in a similar process which extended over the liver, spleen and on to the wall of the intestine. No primary site was found. The tumor involved the visceral pleura on the right and left and showed little invasive tendency. It was composed partly of loosely arranged large polyhedric cells with abundant cytoplasm, and in places there was a tendency to papillary formation with occasional gland imitation; the latter structures seem to consist of flattened tumor cells enclosing mucoid secretions, the nuclei were pleomorphic and hyperchromatic. The thickened liver capsule was made up of tumor tissue showing no invasion. Cell structure was like that found in the pleural tumor. Tumor nodules in the intestine showed the same histologic pattern as the pleura. Diagnosis: Mesothelioma involving serous membranes of the abdomen and chest.

Case 5: J. D. McK., a 32 year old white man was admitted March 12, 1948, with a 12 day history of right chest pain and dyspnea. X-ray film showed right massive pleural effusion. Thoracentesis yielded 3000 cc. of bloody fluid. Surgery was advised but he declined. He was re-admitted on August 1, 1948, with increased chest pain and dyspnea. Exploratory thoracotomy August, 13, 1948, with resection of the right lower and right middle lobe was done. His course was slowly downhill for the next several months, with increasing dyspnea, weakness, nausea and vomiting and severe chest pain. He expired on March 24, 1949. The pleural membrane consisted of spindle cells and reticular cells without stroma. One hilar lymph node showed complete loss of normal architecture and large reticular cells. Diagnosis: Diffuse mesothelioma of the pleura.

Case 6. P. B. L., a 24 year old white man, was admitted June 11, 1956, with a one week history of sudden onset severe left chest pain. He gave a history of left spontaneous pneumothorax three years previously with no sequelae. X-ray film on admission showed massive left pleural effusion. Aspiration yielded grossly bloody fluid. At thoracotomy June 15, 1956, left upper lobectomy was done. He returned October 25, 1956, with recurrent pain and evidence of new tumor in the left thorax. He was explored November 5, 1956 with the finding of extensive visceral, parietal, diaphragmatic and pericardial involvement by tumor. He expired November 23, 1956. The pleura showed a markedly thickened fibrous wall which was relatively vascular in some areas. There were masses of neoplastic cells which were closely packed, very cellular and had little cytoplasm. The nuclei were large, tended to be oval and had prominent nucleoli. No tumor was seen beyond the capsule of the lung. The remainder of the lung was normal. Diagnosis: Diffuse mesothelioma of the pleura.

Solitary Mesotheliomas

Case 1: F. L., a 59 year old white man, was admitted December 8, 1952, because a 10 cm. solitary round mass in the right lower lung field had been found on x-ray film inspection (Fig. 4), in June 1952, He had no complaint. Exploratory thoracotomy was done December 8, 1956, with removal of a pedunculated tumor arising from the basal segment of the right lower lobe in the oblique fissure. There was no evidence of spread. He has been followed to date with no sign of recurrence. The tumor was composed of rather cellular fibrous connective tissue with moderately pleomorphic spindle cells. Mitroses were readily seen. Large patchy areas of necrosis were present. Diagnosis: Solitary mesothelioma of the pleura (malignant).

Case 2: H. T. DeB., a 58 year old white man, was admitted on October 20, 1956, because of a large solitary tumor in the left lower lung field. This was first noted on the x-ray film in 1953. He had no complaint. X-ray film showed no increase in size of the tumor over the two year period. Exploratory thoracotomy on November 2, 1955, was carried out with excision of a pedunculated tumor arising from the visceral pleural of the lingular and anterior segment of the left upper lobe. There was no evidence of spread. He has shown no recurrence to date. There was marked variation in histology. In general, it was composed of dense fibrous tissue with some cellular areas appearing even papillary. Diagnosis: Solitary mesothelioma of the pleura (benign).

Both the diffuse and solitary mesothelial tumors are usually not diagnosed until surgical exploration. There were certain suggestive findings both in the history and on physical and by x-ray film which are helpful. Table II shows these findings in our cases.

Diagnosis

Diffuse Mesothelioma

The diagnosis of these tumors presents the same problems as any intrapleural neoplasm or undiagnosed pleural effusion. Suggestive, we believe, is the finding of massive pleural effusion associated with nodulations on the thoracic wall or on the surface of the lung parenchyma. Bloody effusion, as found in each of our cases, is highly suggestive of this type of tumor. It is rather uncommon in metastatic carcinoma to the pleura to observe as bloody an effusion as was noted in our cases of diffuse mesothelioma. Rapidity of onset of symptoms was characteristic of four of our six cases and we believe is of some diagnostic value. The longest duration of symptoms prior to the patient seeking hospitalization or medical care was three months in two cases. In three out of six cases it was less than two weeks, while the remaining case was approximately one month. The significance of prior history of spontaneous pneumothorax is difficult to evaluate. Eisenstadt[7] reports such an association in his case. Two out of our six cases had such a history, both had occurred on the same side as their tumor. Dyspnea was present in all our six cases but is probably not of any great diagnostic aid. Chest pain likewise was present in all and we believe is of considerable value. It was characteristically of a pleuritic nature. We believe the diagnosis of diffuse mesothelioma must be based on exclusion of metastatic sites plus the clinical findings enumerated. Application of tissue culture for confirmation of diagnosis should be considered when such technique is available. Careful autopsy examination for possible primary tumor is considered to be the only final proof of diagnosis since there is apparently no completely reliable histologic cell pattern.

Solitary Mesothelioma

Solitary mesotheliomas frequently have no chest symptoms. Neither of our two cases had any chest complaint. Known roentgen presence of these tumors for fairly long periods of time has been observed. One of our cases was present at least five months, another at least two years prior to surgery. Frequently as noted by Clagett[8] and Thomas,[9] arthralgia and/or hypertrophic pulmonary arthropathy is associated with these solitary tumors. Sixteen of 24 cases in Clagett's series and four of six in Thomas' series showed such findings. Neither of our two cases had symptoms of arthralgia nor were there any findings of pulmonary arthropathy. The x-ray findings are usually that of a solitary well-circumscribed tumor without satellite nodules, and without effusion. The tumor may arise from any pleural surface. The lesion may be pedunculated or not.[8, 9] Our cases had a solitary tumor. Neither one showed any effusion. Both arose from visceral pleural surfaces.

Treatment and Prognosis

Diffuse Mesothelioma

Prognosis in diffuse mesothelioma is extremely poor, the usual duration of survival being less than one year.[10–14] Surgical excision is of no value unless the tumor can be shown to be limited to a relatively small area of

lung or pleura. There has been no reported five-year cure. X-ray treatment has been of no value. The survival time in our six cases, from onset of symptoms, was 40, 19, 14, 6, 3, and 2 months. In two recent cases we have given nitrogen mustard intravenously, 0.1 mgm, per kilogram of body weight daily for five days. During the same period 60 mgm. ACTH was given intramuscularly four times a day. In Case 1 (F.F.M.), we felt there was definite palliation after the first and second courses but none later. The courses were given six weeks to two months apart. In the second case (C.L.S.), there was no benefit.

Solitary Mesothelioma

The treatment of choice in solitary mesothelioma is resection or excisional therapy. The results[8-10, 15] have been quite good unless spread is present at the time of resection. Even histologically malignant tumors have a good prognosis if no local spread is evident. Malignancy of a solitary tumor is based on either evidence of metastases to the local lymph nodes or to a histologic appearance of moderate cellular variability and frequent mitosis. Histologic appearance of malignancy is unreliable as the prognosis is quite good. One of our cases (F.L., Case 1) was thought to show considerable mitotic activity while the other one did not. Both of these patients have shown no evidence of recurrence to date, a matter of four years and one year, respectively.

The diffuse type of tumor is always malignant and it metastasizes usually only by local extension. These tumors are characteristically not very invasive and usually do not metastasize beyond the mediastinal nodes. Distant metastases are extremely rare, and did not occur in any of our cases. The diffuse type of tumor may extend into the peritoneal cavity or the opposite pleural cavity. Mesothelioma, both solitary and diffuse, of the peritoneal cavity is reported and is believed to be the same tumor as the pleural type. One of our cases showed diffuse pleural and peritoneal involvement, the primary site was not definitely determined.

SUMMARY

(1) Eight cases of tumor of the pleural are presented. All are believed to be of mesothelial origin. Six were diffuse, two solitary. One diffuse tumor may have been primary in the peritoneum with spread to the pleura. All cases with diffuse tumors are dead two to 40 months from onset of symptoms. Both cases with solitary types are living one year and four years after surgery.

(2) The diffuse tumor must be differentiated from metastatic carcinoma. This is done by exclusion of all possible primary sites. A fairly typical clinical picture is highly suggestive. This consists of rapid onset of symptoms, marked dyspnea, pleuritic type pain, and massive bloody pleural effusion.

RESUMEN

1. Se presentan och casos de tumores de la pleura. Se cree que todos son del tipo mesotelial. Seis feuron difusos, dos solitarios.

El tumor difuso puede haber sido primario en peritoneo y propagado a pleura. Todos los casos de tumor difuso murieron de dos a 40 meses después del principio de los síntomas. Ambos casos de tumor solitario viven un año y cuatro años después de la operación.

2. El tumor difuso debe ser diferenciado del carcinoma metastático. Esto se hace por exclusión de todos los lugares de posible primario.

Un cuadro clínico bastante típico es sugestivo y consiste en principio rápido, de los síntomas, disnea acentuada, forma pleurítica del dolor y derrame pleural sangunilento y abundante.

RESUME

1. Les auteurs présentent huit cas de tumeurs de la plèvre. Ils pensent que toutes sont d'origine endothéliale. Six d'entre elles étaient diffuses, deux isolées. Une des tumeurs diffuses était un cancer primitif du péritoine, métastasé à la plèvre. Tous les malades atteints de tumeurs diffuses sont morts de deux à 40 mois après l'apparition des premiers symptômes. Ceux qui avaiaent été atteints de tumeurs isolées sont encore en vie un an et quatre ans après intervention.

2. On peut différencier la tumeur primitive diffuse du cancer métastatique. Il faut pour cela éliminer toutes les localisations primaires possibles. Il existe un tableau clinique vraiment typique et hautement évocateur. Il comporte l'apparition rapide des symptômes: dyspnée accentuée, douleur thoracique de type pleural, et épanchement pleural hémorragique important.

ZUSAMMENFASSUNG

1. Wiedergabe von 8 Fällen von Pleuratumoren. Von allen wird angenommen, dass sie mesothelialen Ursprung sind. 6 waren diffus, 2 solitär. Ein duffuser Tumor kann primär peritonealen Ursprungs gewesen sein mit Aussaat auf die Pleura. Alle Fälle von diffusen Tumoren sind gestorben 2 — 40 Monate nach Beginn der Symptome. Beide Fälle von solitären Typ leben 1 Jahr und 4 Jahre nach der Operation.

2. Der diffuse Tumor muss differentialdiagnostisch abgegrenzt werden vom metastatischen Karzinom. Dies geschieht durch Ausschluss aller möglichen primären Lokalisationen. Ein leidlich typisches klinisches Bild ist in hohem Masse verdächtig. Es besteht in raschem Einsatz von Symptomen, ausgeprägtert Dyspnoe, pleuritischem Typ von Brustschmerz und massivem, blutigem pleuralem Erguss.

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Four to Fifteen Years Follow-up Study on 387 Cases of Pulmonary Tuberculosis Discharged in 1942 through 1953*

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Introduction

Since the introduction of specific drugs great advances in the treatment of pulmonary tuberculosis have been made, and some of the older methods of treatment have been almost abandoned. These advances can be measured most effectively by comparing the long-term follow-up status of patients treated in different ways. It is also felt that an analysis of the late results obtained in patients followed for many years might reveal much information of value in guiding the future handling of this disease.

The purpose of this paper is to present and analyze the results of four to 15 years follow-up study on 387 cases of pulmonary tuberculosis discharged from Piedmont Sanatorium in 1942 to 1953. This was accomplished with the cooperation of the local health departments serving the counties and cities of Virginia.

Materials and Methods

The present study is concerned with an arbitrarily selected group of patients with a diagnosis of pulmonary tuberculosis among 2,432 consecutive discharges from Piedmont Sanatorium, beginning January 1, 1942, through December 31, 1953. All patients are American Negroes, varying in age from 15 to 55 years at the time of discharge. Those over 55 years are not included because many of the older age group become incapacitated by other chronic diseases. Children are not included because in a large percentage of this group the lesions were primary.

An attempt was made to choose at random a comparable number of patients who were treated by the various methods as shown in the tables.

Follow-up letters were sent to each patient's local health department, where the patients have been followed with the assistance of the family physician since discharge. The following information was requested: present state of health; ability to work; additional treatments after discharge, if any; the results of bacteriologic and roentgenographic examinations; whether relapse occurred and, if so, at what time; date of death and cause, if death occurred. The authorized doctors and public health nurses in each clinic completed the above questionnaires from their records and interview with each patient.

Of the 630 follow-up letters, it was possible to obtain information which is available for analysis on 387 (61 per cent) patients. No information was available concerning the remainder, because they had moved to another locality and could not be traced.

The 387 have been classified according to sex, age at the time of discharge, types of treatment during hospitalization and duration of follow-up

*From the Commonwealth of Virginia, Piedmont Sanatorium.

TABLE I

STATUS BY SEX, AGE AND STAGE OF DISEASE ON ADMISSION

Sex and Age	All Stages						Min.			M. A.			F. A.		
	No. of Cases	F	P	S	D	Per Cent	No. of Cases	D	Per Cent	No. of Cases	D	Per Cent	No. of Cases	D	Per Cent
Men															
15-25	56	30	8	4	14	25.0	7	1		23	3		26	10	
26-35	58	28	9	4	17	29.3	10	—		14	2		34	15	
36-45	51	19	9	6	17	33.3	8	—		6	2		37	15	
46-55	29	8	1	5	15	51.7	1	—		6	4		22	11	
Total	194	85	27	19	63	31.9	26	1	3.8	49	11	22.4	119	51	42.9
Women															
15-25	76	27	17	1	31	40.8	6	1		23	7		47	23	
26-35	79	38	20	2	19	24.1	8	—		21	3		50	16	
36-45	27	12	6	3	6	22.2	1	—		10	1		16	5	
46-55	11	2	5	1	3	21.4	2	1		3	—		6	2	
Total	193	79	48	7	59	30.6	17	2	11.8	57	11	19.3	119	46	38.7
TOTAL	387	164	75	26	122	31.5	43	3	6.9	106	22	20.5	236	97	40.8

Min. — Minimal

M. A. — Moderately Advanced

F. A. — Far Advanced

F — Full time work
P — Part time work
S — Sick
D — Dead

period in Table I. The group consists of 194 men and 193 women. The age distribution is mostly in the group of 15 to 35 years. The duration of follow-up of the bed rest alone and pneumothorax groups are mostly for over 10 years, while that of lobectomy and pneumonectomy groups are limited to eight years. Of the 387 patients, 43 were classified on admission as minimal, 106 as moderately advanced and 238 as far advanced disease.

The results are classified into four groups: full time work; part time work; sick and dead. Full time work indicates that the disease is inactive and that the individual is working eight hours or more daily. Part time work indicates that the disease is inactive and the working time is limited to four to six hours daily. "Sick" indicates that the patient is under treatment for active tuberculosis or complications. Deaths are included for both tuberculous and non-tuberculous causes.

Results

The results of the entire series of 387 cases are shown in Table I. One hundred twenty-two (31 per cent) were dead [14 (3.6 per cent) from non-tuberculous causes]; 26 (per cent) were sick and the remaining 239 (62 per cent) were working full or part time. These results are analyzed by the various clinical factors and types of treatment.

Clinical Factors

Sex and Age: There was no significant difference in mortality between men (31.9 per cent) and women (30.6 per cent). However, the mortality for women with minimal lesions was three times higher than that of the men (men, 3.8 per cent, women, 11.8 per cent—Table I). There was marked difference by age. In the men the mortality increased with the age and the mortality of the oldest group (45-55) was approximately twice as high as the youngest group (15 to 25). In the women this trend was reversed and the mortality of the youngest group was approximately twice as high as the oldest group. Several studies have been reported with different opinions.[6, 7, 21]

Extent of disease: The close relationship between the extent of disease in the lungs and mortality is so well known as to need no comment. As shown in Table II, the mortality was greater with far advanced (40.8 per cent) than with moderately advanced (20.5 per cent) and approximately six times higher than minimal (6.9 per cent). These relationships were true regardless of sex, age, and types of treatment.

Cavity size and location: There was a definite correlation between the absence or presence of cavitary lesions, as well as their size and location, concerning the mortality rates. One hundred and fifty-nine patients with no cavity showed a mortality of 11.9 per cent, while 228 with cavities showed a mortality of 45.2 per cent. The size of cavity (total diameter of all cavities) plays an important role and the larger the cavity, the higher the mortality rate. This is in accord with the widely accepted point of view which considers cavitation to be an unfavorable prognostic factor. Some observers, however, do not agree with this point of view.[7-9]

There was no demonstrable relationship between the unilateral location of the cavity and the results attained. There was a minor difference between the cavities in the right lung (44.2 per cent) and the left (38.4 per

TABLE II

STATUS BY GROUPS OF TREATMENT AND STAGE OF DISEASE ON ADMISSION

Treatment	All Stages						Min.			M. A.			F. A.		
	No. of Cases	F	P	S	D	Per Cent	No. of Cases	D	Per Cent	No. of Cases	D	Per Cent	No. of Cases	D	Per Cent
Bed Rest	89	34	5	2	48	52.8	17	2	11.8	23	6	21.1	49	40	81.8
PNX (18.6 per cent with chemo)	75	23	12	2	38	50.7	6	1	16.7	24	10	41.7	45	27	60.6
PNM (80 per cent with chemo)	50	15	11	9	15	30.0	—	—	—	11	2	18.2	39	13	33.3
THOR (66.6 per cent with chemo)	50	20	16	3	11	22.0	—	—	—	4	1	25.0	46	10	21.7
Chemo	65	35	18	5	7	10.8	15	—	—	23	2	8.7	27	5	18.5
Lobect. and Seg. Resect.	48	35	9	2	2*	4.2	5	—	—	21	1*	4.8	22	1*	4.5
Pnect	10	2	4	3	1*	10.0	—	—	—	—	—	—	10	1*	10.0
TOTAL	387	164	75	26	122	31.5	43	3	6.9	106	22	20.5	238	97	40.8

Min. — Minimal
M. A. — Moderately Advanced
F. A. — Far Advanced
F — Full time work
P — Part time work
S — Sick
D — Dead

PNX — Pneumothorax
PNM — Pneumoperitoneum
THOR — Thoracoplasty
Chemo — Chemotherapy
Lobect. and Seg. Resect — Lobectomy and Segmental Resection
Pnect — Pneumonectomy
* — Non-tuberculous

cent). However, the presence of bilateral cavitation raised the mortality rate from 41 to 68 per cent.

Bacteriologic findings: Acid-fast bacilli were demonstrated microscopically in the sputum or gastric contents of all cases on admission except for a few with minimal pathology. Analysis of cases by the bacteriologic findings on admission was therefore considered noncontributory.

The bacteriologic status on discharge definitely related to mortality. Eighty-two patients with positive findings on discharge showed a 75.6 per cent mortality, while in 305 with negative findings the mortality rate was only 19.7 per cent. The high mortality of the positive group could be seen throughout all types of treatment. Most of those in this positive group were discharged against medical advice. A few had received maximum hospital benefit and suitable home care was available.

Types of Treatment

Bed Rest Alone: Eighty-nine patients were treated with bed rest alone and 90 per cent of them were followed for nine to 15 years. Of the 89 of this series, 34 were doing full time work; five part time work; two were sick, and 48 (52.8 per cent) were dead (Table II). Among the 48 deaths, four were from non-tuberculous causes.

Among all treatment groups, as a whole, most of the deaths occurred during the first four years after discharge, following which the proportion of annual deaths occurred at a much lower rate. At the end of four years after discharge 76 per cent of deaths had occurred; the remaining 20 per cent from five to 15 years after discharge (Figure 1).

Pneumothorax: Seventy-five patients were treated with pneumothorax and their refills were continued for an average of two years. Forty had right sided pneumothorax, 28 left sided and seven bilateral. Fourteen (18.6 per cent) had chemotherapy (streptomycin-PAS for three to six months). The observation period of this group ranges from six to 15 years.

Of the 75 with pneumothorax, 23 were doing full time work, 12 part time work, 2 were sick and 38 (50.7 per cent) were dead (Table II). Among the 38 deaths, four were from non-tuberculous causes. As tabulated in Table II, surprisingly, the group treated with bed rest alone showed better results for moderately advanced patients, while the better results in far advanced disease were obtained with pneumothorax.

Pleural effusion was the most feared complication. A small transitory collection of fluid in the costophrenic sinus insufficient to cover the hemidiaphragm was not classified as a complication. Of the 75 patients, 24 (32 per cent) were complicated with pleural effusion, most of them constituting empyema. Of the 14 who had chemotherapy, no one developed pleural effusion.

Those in whom effusion developed had a strikingly higher mortality rate (79.2 per cent) than those who did not (37.3 per cent).

The degree of collapse was considered and it was found that the majority of patients who died had been maintained with a collapse of 50 or more per cent. Similar observations were reported by others.[7, 8, 17, 20]

Pneumoperitoneum: Fifty patients were treated with pneumoperitoneum and were followed up for five to 12 years. The refills were continued for an average of two years. Forty (80 per cent) had streptomycin-PAS for

three to six months and the remaining 10 were treated with pneumoperitoneum alone. The majority were far advanced, none was minimal. Peritoneal effusion was not observed.

Of the 50 in the pneumoperitoneum group, 15 were doing full time work; 11 part time work; 9 were sick and 15 (30 per cent) were dead (Table II). One death was from nontuberculous cause.

There were better results in the pneumoperitoneum group, both in moderately advanced and in far advanced disease, than bed rest alone and pneumothorax group. These better results were apparently due to the fact that the majority of the patients in this group received chemotherapy. The mortality of the pneumoperitoneum group, receiving no chemotherapy was 60 per cent although the number of cases was small. Various results are presented by others.[4, 5]

Thoracoplasty:* Fifty patients received thoracoplasty primarily or following unsuccessful pneumothorax (17 patients), pneumoperitoneum or phrenic nerve interruption (five patients). Only 17 of the 50 had no chemotherapy. The majority of these had far advanced disease and were followed from five to 12 years. Twenty-six had right side thoracoplasty and 42 of the 50 had cavitary lesions.

*Surgery was performed at the Division of Thoracic Surgery, University of Virginia Hospital, Charlottesville, Virginia. Surgeons: Dr. E. C. Drash, Dr. G. R. Minor, and their staff.

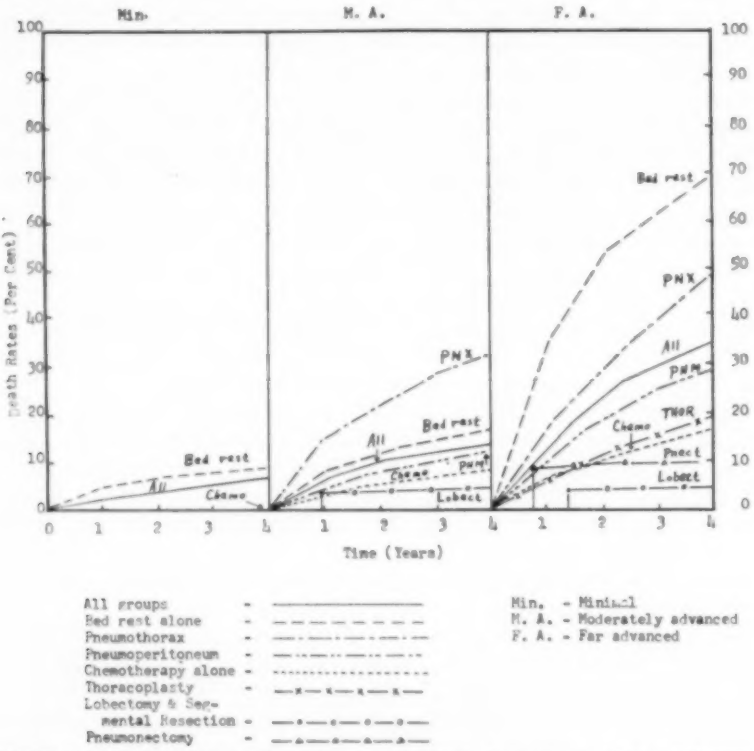

FIGURE 1: Comparative death rates, during first four years after discharge, by groups of treatment and stage of disease on admission.

Of the 50 operative cases, 20 were doing full time work; 16 part time work; three were sick, and 11 (22 per cent) were dead. Eight of the 11 deaths were among those who received no chemotherapy. Two deaths were from non-tuberculous causes. This approximates the results of others.[15, 16] The post-operative hospitalization was longer than six months in all of these cases.

The extent of disease of the contralateral lung at operation was significant from a prognostic standpoint. Fourteen who had no involvement of the contralateral side at operation had a mortality of 7.1 per cent, as compared to 17.2 per cent with minimal and 71.4 per cent with moderately advanced involvement of the contralateral lung.

In the collapse therapy group, there was a marked difference in mortality between the cavitary and noncavitary group. However, there were minor differences in the thoracoplasty group (cavitary group, 25.0 per cent; noncavitary group, 21.4 per cent).

Chemotherapy: Sixty-five patients were treated with chemotherapy alone and most of them were followed up from four to 12 years. Only 30 per cent of this group had cavitary lesions on admission.

Thirty-five were doing full time work; 18 part time work; five were sick, and seven (10.8 per cent) were dead. However, among those with cavitary lesions the mortality was 31.6 per cent. The seven deaths were caused by tuberculosis. No death occurred in the minimal group (Table II).

The analysis suggested that the triple combined regimen (streptomycin, isoniazid, PAS) and isoniazid with PAS were apparently superior to other various regimens. However, definite conclusion can not be drawn from the present materials because of the small number. An important difference was revealed, however, when the duration of chemotherapy was analyzed. None died who received chemotherapy for more than one year but 45 per cent died in the group which received chemotherapy for less than six months and among those treated six to 12 months 9.5 per cent died.

Excisional surgery:* Forty-eight patients received lobectomy (included four segmental resections only) and 10 received pneumonectomy. Twenty-three had right sided lobectomy and six had right pneumonectomy. Of the lobectomy group 56 per cent, and pneumonectomy group 70 per cent had cavitary lesions. Thirty-nine were women and 19 were men. They were followed up from four to eight years.

All had long-term chemotherapy in various combinations and their post-operative hospitalization after excisional surgery was more than six months.

There were two deaths in the lobectomy group. One died of a gun shot wound one year after discharge, and the other died of uremia during pregnancy, two years after discharge. There was only one death in the pneumonectomy group. This patient died of renal disease a year after discharge. Similar results are published by others.[14, 17, 18]

The relations between mortality and the involvement of the contralateral side were not informative due to the small number of patients.

Type of treatment: The relationship between the various therapeutic regimens and the death rates during the first four years after discharge were illustrated in Figure 1.

Although the results of the various therapeutic regimens were not comparable with each other in the minimal cases, the long-term chemotherapeutic regimen appeared to be the superior method. For the moderately and far advanced groups, excisional surgery with chemotherapy was more effective than chemotherapy alone. Collapse, with or without chemotherapy, was inferior to chemotherapy alone. However, the small percentage of cavitary lesions in the chemotherapy group must be considered. Among the collapse therapy group, the best results in far advanced disease were obtained with thoracoplasty, although it was closely paralleled by chemotherapy. Pneumoperitoneum was more effective than pneumothorax in both moderately advanced and far advanced groups, but the additional effect of chemotherapy must be considered. In the moderately advanced disease, unexpectedly, the pneumothorax was less effective than bed rest alone, while more effective in the far advanced group. Similar results were found in the previous paper.[10]

DISCUSSION

Analysis of the present study revealed that the mortality for pulmonary tuberculosis in the younger age group of women, 15 to 25, was definitely high. The probable explanation is the fact that this is the most productive child bearing period of their lives.

The higher mortality of the pneumothorax patients with moderately advanced disease compared with bed rest alone was, also, surprising. However, it must be considered that there were eight with cavitary lesions and seven complicated with pleural effusion, out of the 24 who received pneumothorax. While there were only two with cavitary lesions out of the 23 with moderately advanced disease who received bed rest only (Table II).

The type of treatment appeared to influence significantly the results. It was evident through this study that prolonged chemotherapy for at least one year or more was markedly effective. But, in view of the presence of cavitary lesions, the combination of chemotherapy and excisional surgery seems to produce the best results.

SUMMARY

Three hundred and eighty-seven arbitrarily selected Negro patients with pulmonary tuberculosis who were discharged from Piedmont Sanatorium from January 1, 1942, through December 31, 1953, were followed up from four to 15 years.

The mortality from pulmonary tuberculosis was significantly related to the increasing age in men, the younger ages in women, the extent of disease, the presence or absence of cavity, the size and bilateral distribution of cavities, the bacteriologic findings, the length of chemotherapy and the type of treatment.

The majority of deaths occurred during the first four years after discharge.

RESUMEN

Se observaron durante 4 a 15 años, trescientos ochenta y cuatro enfermos negros arbitrariamente escogidos, los que fueron dados de alta del Sanatorio Piedmont, desde Enero 1 de 1942 hasta Diciembre 31 de 1953.

La mortalidad por tuberculosis guardó relación con la edad más avanzada en los hombres y con la menor edad en las mujeres, así como con la extensión de la enfermedad, la presencia o no de cavidad, el tamaño y la bilateralidad de las cavidades, los hallazgos bacteriológicos, el tiempo de tratamiento y la forma de éste.

La mayoría de las muertes ocurrieron durante los primeros 4 años después de su salida.

RESUME

387 malades de race noire, choisis arbitrairement, atteints de tuberculose pulmonaire, qui quittèrent le Sanatorium Piedmont du Ier janvier 1942 au 31 décembre 1953 furent suivis pendant une période allant de 4 à 15 ans.

La mortalité par tuberculose pulmonaire fut en rapport d'une manière significative avec l'âge élevé chez les hommes, la jeunesse au contraire chez les femmes, avec l'extension de la maladie, la présence ou l'absence de cavité, la distribution uni- ou bilatérale des cavités, les constatations bactériologiques, la durée du traitement chimothérapique et le type de traitement.

La majorité des décès survint pendant les quatre premières années après la sortie de l'hôpital.

ZUSAMMENFASSUNG

Es wurden 387 willkürlich ausgewählte Schwarze mit Lungentuberkulose, die aus dem Piedmont Sanatorium in der Zeit vom 1.1.1942 bis 31.12.1953 entlassen worden waren, nachuntersucht in einem Zeitpunkt von 4-15 Jahre nach der Entlassung.

Die Sterblichkeit an Lungentuberkulose standdeutlich in Beziehung mit dem zunehmenden Lebensalter bei Männern, dem jüngeren Alter bei Frauen, der Ausdehnung der Erkrankung, dem Vorliegen oder Fehlen von Cavernen, der Grösse und beiderseitigen Verteilung von Cavernen, den bakterilogischen Befunden, der Dauer der Chemotherapie und dem Typ der Behandlung. Die Mehrzahl der Todesfälle trat während der ersten 4 Jahre nach der Entlassung ein.

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Disseminated Coccidioidomycosis*

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Coccidioidomycosis is an endemic disease in large parts of the Western and Southwestern United States. Almost every resident in these areas eventually acquires a primary infection, caused by inhalation of the chlamydospores of Coccidioides immitis. In most cases the resulting infection is so mild that it remains unnoticed; only a positive coccidiodin skin test at a later date will reveal that infection has occurred. Other individuals experience respiratory and general symptoms of varying degree as a result of chest lesions such as pneumonitis, cavitation, pleural effusion and spontaneous pneumothorax.

Fortunately, in only a relatively few patients does coccidioidomycosis disseminate to extrapulmonary tissues and organs with the attendant severe morbidity and high mortality rates. It is the purpose of this paper to briefly discuss disseminated coccidioidomycosis, present a few illustrative cases and outline its present day treatment.

Process of Dissemination

When primary infection with Coccidioides immitis has taken place in the lung, a foreign-body type of reaction results in the tissues which contains the infection by a "walling off" process similar to tubercle formation. This defense mechanism—also called "focalization"—begins with the infiltration of lymphocytes about the spherules and endospores. Later, typical foreign body giant cells are formed which contain the organisms. The result is a tubercle which is histologically similar to that formed in tuberculosis. This brings about arrest of the disease at its primary pulmonary site and in regional lymph nodes.

If this process of focalization fails for any reason, then dissemination occurs and both endospores and spherules are carried by the blood and/or lymph stream to other parts of the body where they continue to multiply. Most frequently involved are, in this order:[3] the lungs, lymph nodes, spleen, skin and subcutaneous tissues, liver, kidneys, bones, meninges, adrenals and myocardium. This dissemination usually occurs soon after the infection is acquired, frequently within a matter of weeks and infrequently after months. It rarely occurs in the second year after the infection, although a few such cases have been seen. It is a continuation of the primary infection and due to endogenous reinfection. There is no actual interval or recession of the disease process between the primary and disseminating phases of the infection.

All authors are in agreement that after the acute primary phase is over, the risk of dissemination is almost negligible. Coccidioidal pulmonary cavitation is not in the category of disseminating infection. As a matter of fact, cavitation seems to confer an immunity against dissemination because there is only one case on record in which dissemination occurred

*From Veterans Administration Hospital. Read before the Arizona Inter-VA Hospital Meeting, Phoenix, Arizona, December 7, 1957.

after cavitation had taken place. The nature of this immunity is unknown at present.

Incidence

According to Trimble,[8] not more than 0.1 per cent of the primary cases disseminate in white persons, and women fare even better in this respect than men. Smith's[6] studies among military personnel have shown that among white adult men approximately 1 in 100 with clinical disease undergo extrapulmonary dissemination. Winn[9] has stated that probably not more than 1 per cent of patients will develop dissemination. However, members of the dark skinned races, and particularly the Filipino and the Negro, are distinctly more susceptible to dissemination than are white skinned people. For them Smith[6] found the risk at least 10 times as great, and Winn[7] gives it as 10 to 20 times that of the caucasian races. The exact reason for this lack or defect of the immunological defense is not known. Once dissemination has occurred, the risk of continued dissemination is great, even though spontaneous remissions may occur. Autopsies of those with disseminated infections often show lesions of varying ages and stages of development.

Clinical Picture

With dissemination every body tissue can be involved, with the possible exception of the intestinal tract. Lymphadenitis and osteitis are common, and may produce chronically draining abscesses in the neck, mediastinum, extremities and other body regions. Metastatic abscesses are commonly seen in the liver, kidney, spleen, gonads, adrenals and brain. Pulmonary consolidation may persist and extend, resulting in abscesses and empyema. Myocarditis and pericarditis may develop. Meningitis may run an acute or chronic course; temporary spontaneous remissions are not at all rare, but in the long run the disease always proves fatal. Clinically, dissemination is manifested by an exacerbation of the illness, associated with persistent spiking fever, loss of weight, increasing weakness and toxicity, and evidence of systemic spread. Signs and symptoms in the individual case are determined by the location of the ensuing abscesses.

Diagnosis

Often coccidioidal dissemination mimics miliary tuberculosis, clinically as well as roentgenologically. Differential diagnosis must then rest on the results of serological and bacteriological studies. A positive coccidioidin skin test, especially if recently converted, is an important diagnostic finding. However, many of these severely ill patients have negative skin tests. In these cases skin test conversion to positive during the course of the illness can generally be considered a good prognostic sign, indicating that the body's defense mechanisms are overcoming the infection.

A positive serum precipitin test indicates a recent primary coccidioidal infection, but has no prognostic value. On the other hand, a rising titer of serum complement fixation indicates beginning and/or progressive dissemination if there is complete fixation at a dilution of 1:64 or higher. A persistently rising fixation titer must be viewed as a serious prognostic sign and should be repeated at frequent intervals. Coccidioides immitis

can be readily grown on Sabouraud's medium and C. E. Smith's differential medium from sputum, gastric and bronchial washings, pleural effusion fluid, pus and spinal fluid. Positive blood cultures—as obtained from one of the patients in this series—are only rarely obtained.[1, 4]

Prognosis

The prognosis is always grave for patients with disseminated coccidioidomycosis. Trimble[5] has stated that few patients overcome the infection; dark skinned patients recover rarely, if ever, and white patients but seldom. Smith[6] is more optimistic by saying that from 50 to 60 per cent of these patients succumb to their disease, usually of the fulminating type. This then explains why physicians in the endemic areas are continually searching for an effective remedy and are testing various known medications for their possible effect on Coccidioides immitis.

The following four cases are illustrative of disseminated coccidioidomycosis and were observed at the Tucson Veterans Administration Hospital.

Case 1: A. Q. E., a 45 year old Filipino, developed a tuberculous left upper lobe lesion and basal pleural effusion in July 1954. He also carried a diagnosis of advanced cirrhosis of the liver. Treatment with streptomycin and isoniazid was started and continued after his transfer to Tucson in October 1954. Roentgenograms at that time showed only a fibrous infiltrate in the left upper lobe. A sputum culture, set up in November 1954, grew tubercle bacilli. He did well until January 1955, when his temperature started to spike daily to 102-103° F. At that time the chest x-ray film revealed a new area of pneumonic infiltration in the left base which failed to clear despite therapy. In January 1955, a sputum smear was positive for tubercle bacilli but the culture was negative, whereas several cultures in April and May 1955 were heavily positive. In February 1955, several sputa grew Coccidioides immitis. Coccidioidin skin tests were negative until February 28, 1955, when a 1:10 test was one plus positive. Serum complement fixation on March 14, 1955 was 4 plus positive up to 1:256 dilution and precipitin test was 4 plus positive up to 1:10 dilution. Two weeks later the only change was that the precipitin test was negative in all dilutions. The spinal fluid was negative in all respects in February 1955. A liver biopsy in March 1955 disclosed portal cirrhosis and granulomas compatible with coccidioidomycosis. In March 1955 fine seeding appeared in both lung fields, and from April on there was extensive progressive granular and nodular seeding involving both lung fields. In April 1955, a crusting lesion developed at the tip of the nose, which reached the size of a quarter and, from scrapings of this lesion, Coccidioides immitis was cultured.

The disease continued unchecked (Figure 1) despite supportive treatment, multiple antibiotics, triple sulfa, oil of sassafras and methyl-testosterone. The patient expired on May 31, 1955 with signs of cardiac failure.

Autopsy showed extensive disseminated coccidioidomycosis, involving almost all body organs, including the myocardium. Pulmonary involvement was extremely diffuse and ganulomatous, necrotic and pneumonic in character. Also present was cavitary tuberculosis of the upper lobe of the left lung; the various disseminated coccidioidal areas revealed tubercle bacilli on smears, but only those from an area of the adrenal gland cultured out.

Comment: This is the case of a Filipino whose tuberculosis initially responded well to antimicrobial therapy. When he acquired a superimposed coccidioidal infection, it disseminated quickly and apparently, in turn, caused his tuberculosis to disseminate. Death was due to the impact of the coexisting diseases.

Case 2: L. A. G. was a 47 year old Negro who, on admission on November 1, 1954, gave a three months' history typical of tuberculosis. Chest roentgenogram revealed a left upper lobe lesion. Physical examination was negative except for evidence of consolidation over the left upper chest. It was quickly discovered that in addition to this he was in diabetic acidosis. The diabetes was fairly well controlled with diet and insulin. Numerous studies for tubercle bacilli were negative but sputum smears and cultures and one blood culture (on November 15, 1954) were positive for Coccidioides immitis. His spinal fluid was repeatedly found to be normal. Coccidioidin skin test 1:1000 was 4 plus on admission. On November 28, 1954, complement fixation test was 3 plus at 1:32 dilution and precipitin test was 4 plus at a dilution of 1:10. On December

10, 1954, complement fixation had risen to 3 plus at a dilution of 1:128, and the precipitin test had turned negative.

Later x-ray films showed an increase in the size of the left upper lobe consolidation with formation of a cavity. From late November on, there was diffuse miliary seeding throughout both lung fields which progressed steadily until the time of death (Figure 2). Initially he was treated with streptomycin and isoniazid as a presumptive case of tuberculosis. Because his temperature continued to range daily between 101° and 103° F., various antibiotics were added without the hoped for results. After the diagnosis of disseminated coccidioidomycosis had been established, treatment with THF,* an experimental fungicidal drug, was started. At first 100 mgm. in oil were given intramuscularly every six hours. Because his downhill course continued unabated the dosage was increased to 200 mgm. on December 15, 1954. Again there was no effect on the disease and he expired on December 25, 1954.

Autopsy revealed a large abscess in the left upper lung and smaller ones in both kidneys. There was diffuse coccidioidomycosis throughout all lobes of the lungs, the heart, liver, spleen, adrenal glands, kidneys, bone marrow, lymph nodes and psoas muscle. The central nervous system was uninvolved.

Comment: This is a Negro with fulminating disseminated coccidioidomycosis, complicated by diabetes mellitus. THF, an experimental fungicidal drug, had no effect on the course of the disease.

Case 3: A. S. is a 27 year old white man. In September 1955, he had an abscess of the left buttock excised which supposedly had followed a penicillin injection. Culture of the pus was negative. A chest x-ray film was normal.

He was next seen in January 1956 with swellings over his lower spine, the right arm, left buttock and the skin of the abdomen, which had appeared in mid-December 1955. The skin over these areas was purplish in hue. Chest x-ray film on admission was still normal, but by late January 1956 left hilar lymphadenopathy and an infiltrate extending peripherally from it were visible (Figure 3). Later chest x-ray films showed little, if any, change. By March 1956, x-ray films disclosed two areas of rarefaction in the neck and head of the left femur, each about 5 mm. in diameter, which subsequently did not change.

In July 1957, an area of increased radiotranslucency, 15 mm. in diameter was discovered just above the right hip joint (Figure 4) which represents a granuloma, and a persistent draining fistula appeared over this area. Frequent roentgenograms of the remaining long and short bones failed to reveal additional lesions.

A number of sputum and gastric lavage cultures were negative for acid fast bacilli and fungi. Coccidioidin skin tests were persistently negative with the sole exception of a doubtful positive one in a dilution of 1:10 on May 1, 1957. Complement fixation

*Generously supplied by Organon, Inc., Orange, New Jersey.

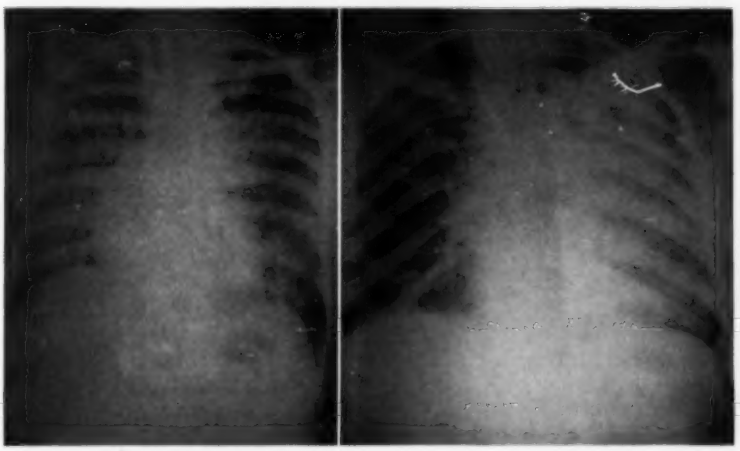

FIGURE 1 FIGURE 2

Figure 1 (Case 1): May 23, 1955. Taken one week before death. There is extensive granular and nodular seeding throughout both lung fields.—*Figure 2* (Case 2): December 22, 1954. Taken three days before death. Reveals very extensive seeding throughout both lung fields. The left upper lobe contains a large cavity.

titers increased steadily up to May 1957, when they apparently stabilized at a level of 2 to 3 plus in a dilution of 1:64; all precipitin tests were negative. A number of biopsies and cultures from the various abscesses of the back, arm, thigh and the fistula over the right hip were repeatedly positive for Coccidioides immitis. Several blood cultures were negative.

Over the past 20 months he has developed a number of subcutaneous and bone abscesses in various locations which required drainage. The fistula over the right hip is still draining. During hospitalization in late 1956 and early 1957 he ran a temperature of up to 100° F. for a few weeks; during April 1957 the temperature peaks reached 101° F. for two weeks and then levelled off. During his latest admission, from August to October 1957, his temperature was normal.

Treatment consisted of evacuation of abscesses, antibiotics for secondary infections and blood transfusions. On August 22, 1957, treatment with Amphotericin B* was started in a dosage of 16.8 mgm. (0.25 mgm./Kg.) intravenously daily. This was continued even though chilly sensations, elevated temperature, nausea and vomiting occurred within a few hours after each injection. The dosage was increased to 33.6 mgm. (0.5 mgm./Kg.) after four days. The reactions continued and the drug was finally stopped on August 29, 1957, after a total of 168 mgm. had been administered. By September 5, 1957, the non-protein nitrogen had risen to 23 mgm. but returned to lower values in two weeks. A second course of Amphotericin B was started on October 15, 1957, with a dosage of 7 mgm.; despite similar reactions, as described before, the dosage was periodically increased. On October 21, 1957 50 mgm. were given; within 18 hours the patient developed an extensive phlebitis extending from the cubital fossa up into the axilla. There was redness, swelling, pain and tenderness, which began to subside after the fourth day. On October 22, 1957, 50 mgm. were given into the other arm, followed by the same reaction. Amphotericin B was then discontinued, after a dosage of 190.5 mgm. for the second course. Thereafter, several urines contained traces of albumin and hyaline casts with pus enclosures. The patient is presently being watched as an outpatient.

Comment: This is the case of a white man with relatively benign disseminated coccidioidomycosis. Treatment with Amphotericin B had to be twice discontinued because of side reactions.

Case 4: R. L. R. is a 31 year old part Indian, part white man. He gave a history of chronic pulmonary disease with fairly frequent acute flareups since 1953. Pneumonia in October 1956 was followed by the appearance of multiple subcutaneous nodules. Gastric lavage cultures at another hospital yielded Coccidioides immitis. In

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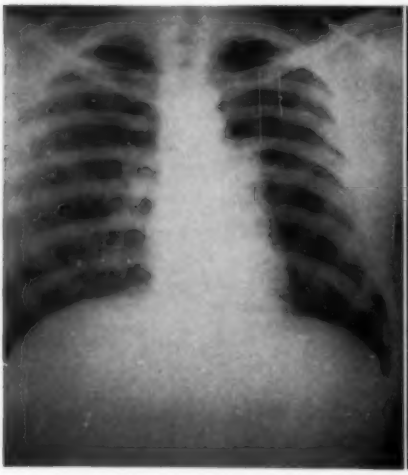

FIGURE 3

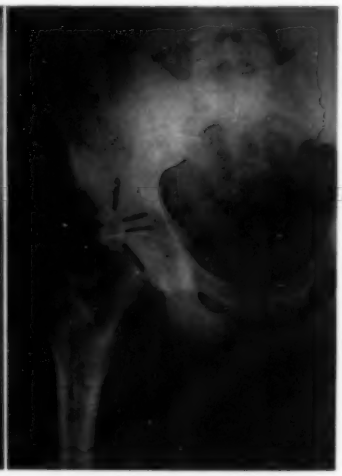

FIGURE 4

Figure 3 (Case 3): January 30, 1956. Left hilar adenopathy and an adjacent area of parenchymal infiltration are present.—*Figure 4* (Case 3): July 23, 1957. There is an area of increased radiotranslucency just above the right hip joint.

December 1956, an abscess over the mid-spine was drained and a body cast applied. During the ensuing months he was given supportive treatment. In July 1957, right sided empyema was diagnosed and open drainage instituted at another hospital. He was then transferred to this hospital.

Examination revealed an emaciated, toxic young man in poor condition with profuse drainage from the right chest and a sinus over the mid-spine. Many smears and cultures of sputum and drainage were negative for Coccidioides immitis and M. tuberculosis with the exception of a sputum culture positive for tubercle bacilli on August 6, 1957. Coccidioidin skin tests were persistently negative until a 2 plus at a 1:10 dilution was obtained in November 1957. Tuberculin test at the same time was repeatedly negative. Complement fixation test was 4 plus at 1:128 dilution in July and August 1957, and rose to 2 plus at 1:256 in September 1957. All precipitin tests were negative. Admission chest x-ray film (Figure 5) revealed extensive infiltration throughout the right lung field with pyopneumothorax, and the left lung exhibited granular seeding throughout. A film of the spine (Figure 6) disclosed severe destruction and compression of the body of the 10th dorsal vertebra and some involvement of the ninth and 11th vertebrae. There were also destructive changes of the 10th and 11th ribs close to the vertebrae.

He was toxic on admission. His temperature spiked to 102° F. daily, he had profuse drainage from the chest and back, and severe anorexia. He was given intensive supportive treatment including multiple blood transfusions. Antibiotics and mycostatin were immediately started, the latter in a dosage of 500,000 units twice daily. During the first month of treatment the patient's temperature came down to about 100° F.

On August 7, 1957, Amphotericin B* was started in daily doses of 9 mgm. intravenously. This was increased several times until a level of 36 mgm. (1 mgm./Kg.) daily was reached on August 21, 1957. The next day prednisolone, 25 mgm. daily, was added, but reduced to 15 mgm. daily after two weeks and continued at this dosage to the present time. After the positive culture for tubercle bacilli was reported, isoniazid and parasal were added on September 10, 1957. Mycostatin was discontinued late in September, that is, after 2½ months; and Amphotericin B on October 2, 1957, after a two months' course. During September and October there was a great deal of improvement in the patient's clinical condition. He became afebrile, his appetite improved, he gained weight and the drainage from the chest and back almost disappeared. The fistula and ulcer over the spine showed much healing, and by late October there was some clearing on the chest x-ray film. A second 90-day course of

*Again generously supplied by E. R. Squibb and Sons.

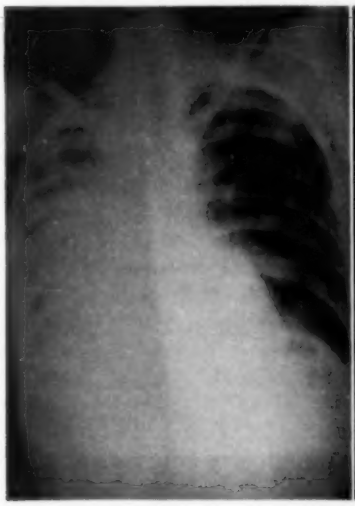

FIGURE 5

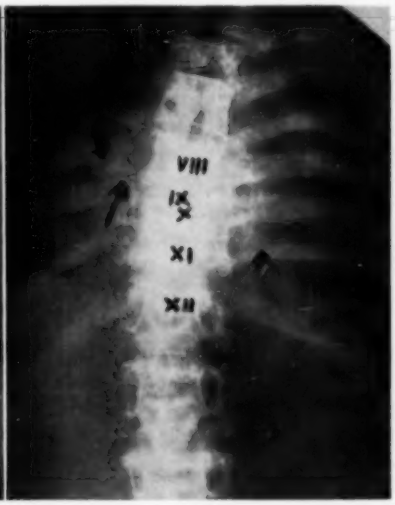

FIGURE 6

Figure 5 (Case 4): July 18, 1957. Shows right pyopneumothorax. The visualized part of the right lung and the left lung field indicate diffuse infiltration, heavier on the right side.—*Figure 6* (Case 4): September 20, 1957. There is severe destruction compression of the body of the 10th dorsal vertebra and some involvement of the ninth and 11th vertebrae. There are also destructive changes of the 10th and 11th ribs close to the vertebrae.

Amphotericin B was resumed on November 13, 1957, with a daily dosage of 36 mgm. intravenously. To date there has been no evidence of toxicity.

Comment: This is a part Indian, part white man, with disseminated coccidioidomycosis who subsequently was found to have also pulmonary tuberculosis. He improved with treatment but, in view of the multitude of drugs administered simultaneously, it can only be said that up to this time Amphotericin B has caused no toxic symptom.

Therapeutic Agents

Because of the grave prognosis for patients with disseminated coccidioidomycosis, many types of treatment have been tried but almost exclusively without success. Conversely, those which appear to have some beneficial effect on the disease must be judged cautiously because "The difficult problem in evaluating these drugs in man is the variability of the clinical course" (Smith).

Among the many therapeutic agents which have been tried clinically without success are: Immunotransfusion, vaccines, coccidioidin, thymol, iodides, arsenicals, colloidal gold and copper, tartar emetic, gentian violet and roentgen irradiation. Newer chemicals and antibiotics such as penicillin, streptomycin, isoniazid, promizole, protoanemonin and stilbamidine have also had no effect. Neither are prodigiosin, mycostatin (when used alone), pregnenolene acetate, sassafras, THF and beta-diethylaminoethyl fencholate of use. Nitrogen mustard is presently being tried with equivocal results. Polymyxin B, aureomycin, chloramphenicol and neomycin inhibit Coccidioides immitis *in vitro* but are of no value clinically. Actidione, an antibiotic, has been used in coccidiodal meningitis but is of questionable value because it inhibits the fungus only in high and, therefore, toxic concentrations.

Lamb[5] reported in 1954 the case of a Negro with disseminated coccidioidomycosis who recovered after prolonged combined administration of large doses of testosterone and meth-dia-mer-sulfonamide. No further follow-up report is available.

Fiese,[2] of Fresno, California, published also in 1954 the apparent cures of one Filipino and two Negro patients with large doses of ethyl vanillate. This drug inhibits Coccidioides immitis, both *in vitro* and *in vivo*. Therapeutic concentrations are relatively non-toxic, but the drug is locally irritating to the empty stomach and occasionally liver and kidney functions are impaired. Furthermore, it is difficult to achieve the necessary therapeutic concentrations because a large daily oral dose—from 32 to 48 grams—is necessary. This difficulty is even more pronounced in those patients severely ill with coccidioidal meningitis or fulminating dissen.inated coccidioidomycosis who need the drug most.

The newest available therapeutic agent is Amphotericin B or Fungizone (Squibb).[7] This antibiotic is formed by a hitherto unidentified species of streptomyces isolated from a soil sample obtained at Tembladora, on the Orinoco River in South America. It is biologically standardized at a rate of 1,000 units per milligram. Chemical analysis has not yet been done. It is insoluble in water, but moderately soluble in water plus sodium lauryl sulfate.

Oral administration, due to poor absorption, requires larger doses than if given by the intravenous route. After oral administration to dogs, Fun-

gizone is excreted in the urine and also eliminated in the feces. The maximal lethal dose in mice was found to be 7.95 ± 0.45 mgm./Kg.

In preliminary assays, the effect of Fungizone and Mycostatin appeared to have been additive on Monilia (Candida albicans) and certain yeasts. In mice, Fungizone alone appeared to have an ameliorating effect on the course of coccidioidomycosis. Fungizone, suspended in glucose and distilled water has been given intravenously in man in total daily doses up to 100 mgm. Blood levels 16 to 18 hours after discontinuing therapy have ranged from 1.15 to 4.0 micrograms per milliliter.

Fungizone, orally and intravenously, has been given successfully to a small number of patients with various manifestations of disseminated coccidioidomycosis. In all of them skin and bone lesions have healed. One patient with meningitis has shown excellent clinical improvement but a possible spontaneous remission must be kept in mind.

The usual oral dosage is 3 to 4 grams daily, in 4 to 6 divided doses but larger doses may be given in advanced cases. Intravenously an initial dose of 0.25 mgm./Kg. should be given over a period of approximately six hours. This dose should be gradually raised to an optimum daily dose of 1 mgm./Kg., depending on the severity of the infection and the patient's tolerance to the medication. Intrathecal administration of 0.5 to 1.0 mgm., diluted in 5 cc. of water, on alternate days, has been used but should be given only in severe cases of meningitis and be restricted to a few injections only.

The initial intravenous administration of Fungizone is usually associated with a febrile response, often accompanied by chills. These reactions diminish with successive infusions and can be relieved by aspirin and antihistaminics. Headache, nausea and vomiting are also early manifestations and can be offset by lowering the dosage. During prolonged or excessive parenteral administration blood urea nitrogen and non-protein nitrogen have been observed to increase to abnormal levels, usually without other apparent evidence of renal impairment. Phlebitis occasionally follows intravenous infusion. It is related to insufficiently diluted solutions and/or excessively rapid injection through narrow-gauge needles.

It appears that Amphotericin B or Fungizone is a hopeful new agent in the treatment of disseminated coccidioidomycosis. Additional and carefully controlled observations are necessary which must take cognizance of the natural development of this disease with its fairly common spontaneous remissions, before a final opinion as to its therapeutic value can be formed.

SUMMARY

1. Most residents of the North American areas endemic for Coccidioides immitis acquire a generally mild primary infection. Dissemination occurs in only about one per cent of white persons and in 10 to 20 per cent of dark skinned people.

2. Dissemination follows failure of the body to "focalize" the disease at its primary site. It is an endogenous reinfection and comes on shortly after the primary infection of which it is a continuation. Coccidioidal pulmonary cavitation seems to confer immunity against dissemination.

3. Dissemination involves every body tissue, excepting the intestinal tract. Multiple abscesses, spread widely throughout the body, are frequent, meningitis somewhat less so. The latter not infrequently shows temporary spontaneous remissions of varying duration.

4. The diagnosis rests mainly on bacteriological and serological studies rather than on clinical findings. Anergy renders the coccidioidin skin test unreliable in the disseminated form of the disease. The prognosis is grave because the mortality rate is at least 50 to 60 per cent, especially in non-white individuals.

5. Many therapeutic agents have been tested unsuccessfully. A new antibiotic, Amphotericin B or Fungizone, has benefited a small number of patients. It has, however, various undesirable side reactions which lead to interruption or discontinuation of its use in quite a few patients.

RESUMEN

1. La mayoría de los residentes en las áreas de Norteamérica donde la coccidiodes immitis produce endemia, adquieren generalmente una infección benigna. La diseminación ocurre en sólo 1 por ciento de las personas de raza blanca y de 10 a 20 por ciento en los de piel obscura.

2. La localización sigue a la falta de eficacia del organismo para "focalizar" la enfermedad en su lugar de primera implantación. Es endógena esta reinfección y sobreviene poco después de la infección primaria de la que una continuación. La cavidad pulmonar de coccidiosis parece conferir inmunidad contra la diseminación.

3. La diseminación compromete todo tejido con excepción del tubo intestinal. Los abscesos múltiples diseminados en todo el cuerpo, son frecuentes; la meningitis lo es algo menos. Esta última frecuentemente muestra remisiones espontáneas de duración variable.

4. El diagnóstico se basa principalmente en los estudios serológicos y bacteriológicos más bien que en los hallazgos clínicos. En las formas diseminadas la anergía hace que las pruebas cutáneas de coccidioidina sean de poca confianza. El pronóstico es grave porque la mortalidad es por lo menos de 50 a 60 por ciento especialmente en los sujetos de razas otras que la blanca.

5. Se han ensayado muchos agentes terapéuticos sin resultados. Un nuevo antibiótico la Amfotericina B o Fungizona ha sido benéfico para un pequeño número de enfermos. Sin embargo tiene reacciones colaterales que conducen a la interrupción o suspensión de uso en algunos enfermos.

RESUME

1. La plupart des habitants des zones d'Amérique du Nord où existe une endémie de coccidioidomycose font une primo-infection généralement faible. La dissémination de la maladie ne frappe que 1% des individus de race blanche et 10 ou 20% de ceux de race noire.

2. La dissémination est la conséquence de l'impossibilité de l'organisme à localiser l'affection dans son siège pulmonaire primitif. C'est une réinfection endogène et elle apparait peu après l'infection initiale dont elle est la continuation. Le processus cavitaire pulmonaire du à la coccidioidose semble conférer une immunité contre la dissémination.

3. La dissémination s'étend à tous les tissus, sauf à l'intestin. Les abcès multiples, largement diffusés dans tout le corps, sont fréquents, toutefois la méningite l'est moins. Il n'est pas rare que cette dernière comporte des rémissions spontanées temporaires de durée variée.

4. Le diagnostic repose sur les études bactériologiques et sérologiques plus que sur les constatations cliniques. L'anergie annule le test cutané à la coccidioidine dans la forme disséminée de la maladie. Le pronostic est sévère, le taux de mortalité étant d'au moins 50 ou 60%, surtout chez les individus qui ne sont pas de race blanche.

5. Beaucoup de médications ont été testées sans succès. Un nouvel antibiotique, l'amphotéricine B ou fungizone, a eu un effet favorable sur un petit nombre de malades. Il a provoqué cependant quelques réactions d'intolérance qui ont amené l'interruption ou la discontinuité de son utilisation chez plusieurs d'entre eux.

ZUSAMMENFASSUNG

1. Die meisten Bewohner derjeniger Bereiche von Nordamerika, in denen jetzt Coccidioides immitis endemisch vorkommt, machen eine allgemeine milde Primärinfektion durch. Eine Dissemination erfolgt nur bei ungefähr ein Prozent der Weissen und bei 10 bis 20 Prozent der farbigen Bevölkerung.

2. Eine Dissemination ist die Folge eines Versagens des Körpers, die Krankheit auf einen Herd zu begrenzen an ihrem primären pulmonalen Sitz. Es handelt sich um eine endogene Reinfektion, die kurze Zeit nach der Erstinfektion auftritt, deren Fortsetzung sie darstellt. Eine durch Coccidioides bedingte pulmonale Cavernenbildung scheint eine Immunität gegen eine Dissemination zu verlangen.

3. Die Dissemination betrifft jedes Körpergewebe, ausgenommen den Intestinaltrakt. Multiple Abszesse, weit über den Körper verstreut, kommen häufig vor, die Meningitis etwas weniger. Letztere zeigt nicht selten temporäre Spontanremissionen von verschiedener Dauer.

4. Die Diagnose beruht mehr als auf klinischen Befunden hauptsächlich auf bakteriologischen und serologischen Untersuchungen. Infolge Anergie wird der coccidioidin Hauttest unzurverlässig bei der disseminierten Krankheitsform. Die Prognose ist ernst, weil die Sterblichkeitsziffer wenigstens 50 bis 60 Prozent beträgt, besonders bei farbigen Individuen.

5. Viele therapeutische Stoffe wurden ohne Erfolg erprobt. Ein neues Antibiotikum, Amphotericin B oder Fungizone war bei einer kleinen Zahl von Patienten heilsam. Es besitzt jedoch verschiedene unerwünschte Nebenwirkungen, die zu einer Unterbrechung oder Beendigung seiner Anwendung bei nicht wenigen Patienten führt.

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Isoniazid and Para-Aminosalicylic Acid Toxicity in 513 Cases: A Study Including High Doses of INH and Gastrointestinal Intolerance to PAS*

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Introduction

In early 1956 it was demonstrated that the combination of isoniazid (INH) and para-aminosalicylic acid (PAS) provided a superior statistically significant treatment result in far-advanced and large cavitary tuberculous lesions.[1] This study made a comparison between INH-PAS, streptomycin (SM)-INH, and SM-PAS (all SM was given intermittently). This year the use of high doses of INH in the treatment of pulmonary tuberculosis was again emphasized.[2] Available data indicate that PAS competes with INH in the process of acetylation of both drugs. The combination of both drugs results in a higher serum level of biologically active, free, unacetylated INH.[3] Thus, by adding PAS and elevating the dose of INH to 10 or 16 milligrams per kilogram of body weight per day instead of the more usual dose of about 5 milligrams per kilogram per day, an effective serum concentration of "free" INH can be attained. It is suggested that this level be at least 0.8 micrograms per milliliter of serum six hours after one-third of the total daily dose of INH and PAS is given.[4]

If one accepts that INH and PAS, with more elevated doses of INH, constitute one of the most effective antituberculous chemotherapeutic drug combinations at present, then one must consider the potential effects of drug toxicity or allergy and drug intolerance. There are many reports to document the multitude of allergic or toxic reactions due to PAS.[5-8] However, detailed studies regarding the incidence and cause of gastrointestinal intolerance due to PAS are not readily found. Many generalities can be found regarding the "accepted"' high incidence of intolerance to PAS. A quoted example is, "The well known symptoms of nausea, abdominal distress, vomiting, and diarrhea are a common experience."[5] One of us has seen gastrointestinal intolerance to PAS mount as high as 50 per cent on a single tuberculosis ward. It was of interest to note that this rate was reduced to about 15 per cent when the attitude of the ward doctor toward the "inevitable intolerance to PAS" became changed. It is believed that intolerance to PAS is directly related to the purity of the drug, and the attitude of the physician prescribing the drug which induces a iatrogenic intolerance in the patient. At two recent informal "PAS Meetings,[9] the problems of drug purity were discussed. Para-aminosalicylic acid varying in age from six months to three years was tested and revealed

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degrees of deterioration between 35 and 70 per cent. Para-aminosalicylic acid is a relatively unstable compound which decomposes under the influence of heat, light, moisture, time, and catalytic action of heavy metals. It has been suggested that the administration of freshly prepared and adequately controlled PAS would reduce the amount of the decomposition products of PAS that are related to gastrointestinal intolerance.

The toxic effects due to INH have been variable, but principally neurological.[10, 11] No great problem has existed with the use of doses of INH in the range of 300 milligrams per day. On much higher daily dosages, up to one-third of the patients developed peripheral neuropathies.[10] The use of pyridoxine has subsequently proved to reduce or prevent neuropathies due to INH. Nevertheless, there are many physicians who maintain concern regarding the prolonged use of high doses of INH.

In light of the aforementioned comments, the purpose of this report is to suggest that PAS and elevated doses of INH, with pyridoxine, can be given to patients over prolonged periods with relative safety.

Materials and Methods

All patients treated at this hospital with INH or PAS during a nine month period (November 1, 1956 to August 1, 1957) were reviewed. This study comprises a total of 513 all of whom received INH as part of their treatment. Paraaminosalicylic acid was also administered to 303 of these 513 patients. The majority were given combined chemotherapy consisting of INH and PAS, or INH and SM. A small number of cases received triple drug therapy (INH, PAS and SM). Of the 513 who received INH, 329 (64 per cent) were given doses of 10 or 16 milligrams per kilogram of body weight per day. The remaining 184 (36 per cent) were given 300 milligrams of INH per day. All patients taking either 10 or 16 milligrams per kilogram of INH per day also received 100 milligrams of pyridoxine once daily. No pyridoxine was administered with doses of only 300 milligrams of INH per day.

The observation period on chemotherapy in these 513 patients at the time of this study was as follows. One hundred and eleven (21.6 per cent) cases received one to two months of therapy, 60 (11.7 per cent) two to three months, 133 (26 per cent) three to six months and 209 (40.7 per cent) received over six months of therapy.

In four of the five cases that exhibited toxicity to INH, the same toxic reaction was reproduced by a second course of therapy. One was accidentally given 20 to 25 milligrams of INH per kilogram daily for four to five days. The dizziness produced in this patient disappeared immediately when a lower dose was administered. The same toxic symptoms were reproduced in 22 of the 26 cases reacting to PAS. In four cases (three with G. I. intolerance and one with hematemesis) PAS was not administered a second time.

All receiving isoniazid were given this drug in the form of tablets. Paraaminosalicylic acid was administered in the form of the sodium salt. No chemical additive was introduced. In order to minimize deterioration of PAS and attempt to reduce gastrointestinal intolerance, the following control measures were instituted. An order was placed with the manu-

facturer for an estimated six weeks supply of PAS. This was delivered in polyethylene packets, sealed in nitrogen instead of air, and contained 5.57 grams of sodium para-aminosalicylate (equivalent to four grams of para-aminosalicylic acid). The date of manufacture was stamped on each lot of PAS, and the manufacturer arbitrarily indicated a 120 day expiration date. By replenishing the supply of PAS every six weeks, it was possible to deliver this drug to patients within two months of its manufacture. Precautions were taken to eliminate the possibility of mixing new orders of PAS with the waning previous order at this hospital. Exposure of the drug to light, heat, and moisture were controlled within practical limits by the pharmacy office. One packet of PAS was administered to each patient three times daily (total dose equivalent to 12 grams of para-aminosalicylic acid daily). Each packet was opened at the bedside and mixed with 3 to 4 ounces of water or fruit juice. The patient drank the dissolved medication immediately and followed it with a mouthful of fresh water.

TABLE I

TOXIC REACTIONS TO INH OCCURRING IN 513 CASES

Type of Reactions	No. of Cases	Interval Between Onset of Therapy and Toxicity in Days
Dizziness	2	7 and 10
Chills, fever and rash. Tachycardia, jaundice, rash, and fever ocurred with second dose of INH	1	49
Chills, fever, headache, tachycardia, nausea and vomiting	1	X*
Fever and rash	1	28

*Patient discharged before time of onset of toxicity recorded.

TABLE II

TOXIC REACTIONS TO PAS OCCURRING IN 303 CASES

Type of Reactions	No. of Cases	Interval Between Onset of Therapy and Toxicity in Days
Fever	2	7 and 10
Rash	1	14
Fever and rash	2	12 and 26
Exfoliative dermatitis	1	28
Chills, fever, headache, tachycardia, nausea & vomiting	3	1, 7, and 28
Chills, fever & somnolence	1	7
Chills, fever, rash, somnolence & eosinophilia	1	1
Gastrointestinal upset	15	2, 3, 4, 4, 12, 14, 16, 19, 24 25, 30, 40, 45, X*
Hematemesis (no evidence of peptic ulcer)	1	X*

*Patient discharged before time of onset of toxicity recorded.

Observations

In Table I, data are tabulated with reference to five cases exhibiting toxic reactions to INH. All five drug reactions occurred in patients receiving 10 or 16 milligrams of INH per kilogram per day. The majority of the recorded toxic reactions were manifested within one month of the onset of therapy. The incidence of toxicity due to INH in all 513 cases was 0.97 per cent. Since all five toxic reactions occurred in patients receiving elevated doses of INH, the incidence of toxicity noted in 329 cases on elevated doses of INH was 1.52 per cent.

In Table II, 27 reactions to PAS due to allergy or gastrointestinal intolerance were noted in 303 patients. Twenty (74 per cent) of these toxic reactions were recorded to have occurred before one month of therapy was completed. The incidence of all forms of toxicity due to PAS in these 303 patients was 8.9 per cent. Sixteen (5.3 per cent) exhibited gastrointestinal complications due to PAS. The remaining 12 (4 per cent) were considered to have had allergic disorders as illustrated in Table II. If the one case with hematemesis is eliminated, it will be noted that 15 of 303 (4.9 per cent) developed the gastrointestinal symptoms of anorexia, nausea, vomiting or diarrhea that have been so frequently associated with PAS in the past. Vomiting rarely occurred. Anorexia and nausea, or diarrhea were noted more frequently. The three in Table II with chills, fever, headache, tachycardia, nausea, and vomiting were accepted as allergic reactions to PAS. The nausea and vomiting were not initial symptoms, but occurred after chills, fever, headache and tachycardia were well established.

DISCUSSION

When it was reported that the combination of INH and PAS constituted a more superior drug combination than intermittent SM with INH or PAS, then PAS no longer became a second choice drug. A primary need for PAS developed. Some physicians now became interested in the incidence and cause of gastrointestinal intolerance due to PAS. The specific cause of this intolerance has not been absolutely proved, but strong clinical and biochemical evidence exists suggesting that the cause rests with the decomposition products of this unstable drug. It is important in this respect to emphasize that only 4.9 per cent of patients in this present report developed the commonly accepted gastrointestinal symptoms due to PAS. The authors firmly believe that this low rate is due to: The methods used to deliver freshly manufactured and controlled PAS to the patient, and the education of the physician to the effect that he need not have to accept a high incidence of gastrointestinal intolerance from PAS.

It is now generally accepted that INH is one of the most important drugs available in treating tuberculosis. This can best be appreciated when one reviews the marked decrease in relapse and mortality rates in miliary, meningeal, and renal tuberculosis after INH was put into use. Present investigation at other institutions and at this institution suggest that elevated doses of INH with PAS offer a distinct therapeutic advantage. One of the purposes of this report is to suggest that elevated doses of INH can be given safely to large numbers of patients for prolonged periods of time, providing pyridoxine is also administered. The small per cent of toxic reactions to INH noted in 513 patients is about equal to the per cent of allergic reactions expected from many numbers of other drugs used in the practice of medicine. It is certainly of interest to note that none of these 513 patients developed a peripheral neuropathy. The only reactions of possible neurological significance consisted of two cases of dizziness. The only truly serious reaction occurring in all 513 patients was the case of jaundice noted in Table I. When a second dose of INH was given, the patient developed a severe toxic hepatitis. The electrocardiogram revealed R-ST changes suggesting a toxic myocarditis. This patient has presently made a full recovery from all toxic signs and symptoms. He had been receiving 10 milligrams per kilogram of INH per day plus 12 grams of PAS per day. After the rash and fever ocurred, both drugs were stopped. Later INH alone was started in lower doses and it immediately precipitated jaundice, rash, fever, and tachycardia. This patient was subsequently successfully desensitized to INH.

It is important to realize that the majority of patients in this study fell within the 20 to 40 year old age group. The incidence of malnutrition, chronic alcoholism and intercurrent disease was very low.

In a study of this nature, it should be mentioned that there are occasional reports referring to the antithyroid action of PAS.[12] No controlled study of thyroid function was made on the 303 patients in this report who received PAS. However, no palpable goiters developed and there was no obvious clinical manifestation of hypothyroidism.

SUMMARY

Toxic drug reactions in 513 patients receiving INH and 303 patients receiving PAS have been reviewed. Sixty-nine per cent were observed for over three months. All had received at least one month of therapy at the time of this study. In 303 patients taking PAS, drug allergy and gastrointestinal intolerance occurred in 8.9 per cent. Only 4.9 per cent developed gastrointestinal symptoms of nausea, vomiting, and diarrhea. Only 0.97 per cent of the 513 patients receiving INH developed toxic symptoms. Toxic reactions that did occur were derived from the 329 cases taking high doses of INH. The per cent toxicity from INH in these 329 cases was 1.52 per cent. By using the methods described in detail, the authors believe that high doses of INH plus PAS can be safely given to large numbers of tuberculosis patients for prolonged periods, provided these patients are otherwise in a state of good nutrition and do not have pre-existing central nervous system or hepatic disease.

RESUMEN

Se han revisado las reacciones tóxicas que se presentaron en 513 enfermos que usaron insoniacida y 303 que tomaron PAS.

Se observaron el sesenta y nueve por ciento por más de tres meses. Todos habían recibido por lo menos un mes de tratamiento cuando se hizo este estudio. En 303 enfermos que tomaron PAS se presentó alergia a la droga y trastornos de intoleramia gastrintestinal en 8.9 por ciento. Sólo 4.0 por ciento tuvieron síntomas gastrintestinales como náusea, vómitos y diarrea. Sólo 0.97 por ciento de 513 enfermos que recibieron HAIN tuvieron síntomas tóxicos.

Las reacciones tóxicas que occurrieron se derivaron de 329 casos que tomaron altas dosis de HAIN. El porcentaje de toxicidad de HAIN en estos 329 casos fué de 1.52 Usando los métodos que en detalle se describen creen los autores que las dosis altas de HAIN más PAS, pueden dase con seguridad a gran múmero de tuberculosos por períodos prolongados siempre que estos enfermos están por otra parte en buenas condiciones de nutrición y no tengan padecimientos previos del sistema nervioso central o afección hepática.

RESUME

Les auteurs rapportent les réactions toxiques à la médication chez 513 malades recevant de l'isoniazide et 303 malades recevant du P.A.S. 69% de ces malades furent observés pendant plus de trois mois. Tous reçurent au moins un mois de traitement pendant le période que couvre cette étude. Chez 303 malades prenant du P.A.S. une allergie à la médication et une intolérance gastro-intestinale survint chez 8,9%. 4,9% seulement présentèrent des symptômes gastro-intestinaux avec nausées, vomissements et diarrhée. 0,97% seulement sur les 513 malades recevant de l'isoniazide furent atteints de symptômes toxiques. Les réactions toxiques que furent notées concernaient les 329 malades prenant de hautes doses d'isoniazide. Le pourcentage de toxicité de l'isoniazide chez ces 329 malades fut de 1,52%. En utilisant des méthodes décrites en détail, les auteurs pensent que de hautes doses d'isoniazide associées au P.A.S. peuvent être données sans danger à un très grand nombre de malades tuberculeux pendant des périodes de temps prolongées, à condition que ces malades soient par ailleurs en état de bonne nutrition et qu'ils n'aient pas une affection nerveuse centrale pré-existante ou une affection hépatique.

ZUSAMMENFASSUNG

Bericht über toxische Arzneimittelreaktionen bei 513 Kranken, die INH bekamen, und 303 Kranken, die PAS bekommen hatten. 69% wurden mehr als 3 Monate beobachtet. Alle waren mindestens einen Monat behandelt worden z.Z. dieser Untersuchung. Bei 303 Patienten, die PAS nahmen, traten Arzneimittelallergie und gastrointestinale Unverträglichkeit in 8,9% auf. Nur bei 4,9% entwickelten sich gastroinestinale Symptome, wie Übelkeit, Erbrechen und Durchfälle. Nur bei 0,97% der 513 mit INH behandelten Patienten entwickelten such toxische Symptome. Toxische Reaktionen, die auftraten, wurden abgeleitet von den 329 Fällen, die hohe INH-Dosen nahmen. Die prozentuale Toxicität durch INH bei diesen 329 Fällen lag bei 1,52%. Unter Benutzung der im Detail beschriebenen Methoden glauben die Autoren, dass hohe Dosen von INH und PAS mit Sicherheit einer grossen Zahl von tuberkulösen Patienten über lange Zeiträume gegeben werden kann, vorausgesetzt, dass diese Kranken sonst in einem gu tem Ernährungszustand sind und dass keine zuvor bestehende Erkrankung des zentralen Nervensystems oder der Leber vorliegen.

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The Significance of Pleural Effusion Complicating Otherwise Operable Bronchogenic Carcinoma

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Bronchogenic carcinoma complicated by pleural effusion which is not attributable to congestive heart failure or systemic disease, presents a difficult problem in management. Especially is this so when the patient appears otherwise suitable for operation. Most surgeons are agreed that the presence of malignant cells in pleural effusion indicates inoperability, but the significance of fluid in which malignant cells are not seen is debatable. Rosenblatt and Lisa[1] state that while pleural effusion may mean secondary involvement of the pleura, they found that 47 cases in their series (22 per cent of those with a pleural effusion) had no evidence of metastatic involvement of the pleura. However, Mayer and Maier[2] believe that pleural effusion usually indicates a lesion beyond the stage of surgical curability. The effusion is sometimes attributed to venous obstruction resulting from tumor compression in which case there may be no metastatic involvement of the pleura. Occasionally this may be true, but experience in this hospital indicates that whether malignant cells are demonstrated or not, the presence of pleural effusion adversely effects the operability and prognosis of patients with bronchogenic carcinoma.

In order to establish the significance of pleural effusion in these otherwise operable patients, the 360 cases of bronchogenic carcinoma seen at Henry Ford Hospital from 1936 through 1955 were reviewed. There were 21 with pleural effusion who had no evidence of secondary spread elsewhere and as far as could be judged clinically, were operable and potentially curable patients. Of these 21 whose ages ranged from 48 to 73 years, 19 were men and two were women. The effusion was present on the left 16 times and on the right five times. Pre-operative thoracentesis was done in most cases and although malignant cells were looked for on six occasions, only one positive fluid was reported. The recognition of malignant cells in pleural fluid is particularly difficult and not too much reliance should be placed on either positive or negative reports. For that reason, although malignant cells were reported in one specimen of pleural fluid, this patient has been included in the series. The amount of fluid present at operation varied from 100 cc. to 2,000 cc. and was straw-colored except for three cases in which it was serosanguinous.

All 21 patients underwent thoracotomy, at which time 17 were found to have mediastinal involvement, while five had obvious pleural secondaries as well. Eleven of these 21 were considered inoperable. The other 10 had pneumonectomy, eight of which were on the left side. In six this was a palliative procedure with subsequent survival varying from one to 24 months. The mean survival time was seven months, compared to a mean survival for untreated bronchogenic carcinoma of four to six-and-a-half months.[3-5] Four patients had pneumonectomy with removal of all recognizable tumor. However, three of these died within six months of

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operation. One died on the third post-operative day of pulmonary edema; the other two of recurrence of their disease. The fourth was a man aged 65 who had a left pneumonectomy performed for a squamous cell carcinoma originating in the left lower lobe. One thousand cc. of straw-colored fluid was present in the pleural space, and microscopic examination of the surgical specimen showed that one subcarinal node was invaded by tumor. Nevertheless, since operation this patient has maintained good health and seven years later still has no evidence of recurrence.

The site of origin of the carcinoma in the 21 patients is shown in Table I.

The poor prognosis in this group of patients is partially explained by the frequency of left-sided lesions. Bignall and Moon[6] report a five year survival of 39 per cent for right-sided lesions compared to 31 per cent for left-sided carcinomas, while Gifford and Waddington[7] give comparable rates of 34 per cent and 22 per cent respectively. The difference in prognosis between carcinoma in the right and the left lung is probably due to the difference in the lymphatic drainage between the two sides. Rouvière[8] demonstrated that the lower two-thirds of the left lung drains into the right paratracheal nodes, and this has been confirmed in dogs by Warren and Drinker.[9] Furthermore, McCort and Robbins[10] have shown that carcinoma in the left upper lobe may also metastasize to the right paratracheal nodes before involving the left paratracheal nodes. There is therefore good reason to believe that the lymphatic drainage of the left lung may be predominantly into the lymphatic channels in the right hemithorax. If before operation cross dissemination has already taken place, the surgeon will be unable to remove all involved glands in the course of a left pneumonectomy.

The same explanation probably accounts for the frequency of left-sided effusion, 16 (76 per cent) in this series were on the left side. For if the lymph channels which drain the left lung and anastomose with those in the right hemithorax are obstructed by tumor, the left paratracheal lymph vessels may be unable to carry the increased lymph flow, with pleural effusion developing as a result. Because the lymph vessels on the right side have a greater capacity and do not become so readily obstructed, right-sided effusions are less common.

Histological examination of the tumors showed that seven were squamous cell, eight were undifferentiated and six were adenocarcinomas. Normally, 60 per cent of bronchogenic carcinomas are squamous cell[6, 7] whereas only 33 per cent of tumors in this series were squamous cell. This would indicate that pleural effusion either develops more frequently, or occurs earlier in the natural history of undifferentiated carcinomas and adenocarcinomas than it does in squamous cell carcinoma.

TABLE I—THE SITE OF ORIGIN OF THE BRONCHOGENIC CARCINOMA IN THE 21 PATIENTS

Right Side	*5*	*Left Side*	*16*
Upper lobe	3	Upper lobe	7
Middle lobe	2	Lingula	1
Lower lobe	0	Lower lobe	8

CONCLUSION

It is apparent that the presence of pleural effusion, whether malignant cells are demonstrated in the fluid or not, is of serious prognostic significance. At thoracotomy, 17 of these patients showed evidence of extrapulmonary spread of their disease, and only one has survived for over two years. It is questionable whether a major procedure such as pneumonectomy, especially in an elderly person, is justified when the chance of cure is so poor.

SUMMARY

Twenty-one cases of bronchogenic carcinoma with pleural effusion occurring as the only manifestation of possible extrapulmonary involvement are reported. All were subjected to thoracotomy, but only one survived for more than two years. It is questioned whether thoracotomy is justified in these patients, even though malignant cells are not demonstrated in the pleural fluid.

RESUMEN

Se relatan veintiún casos de carcinoma bronquiogénico con derrame pleural que ocurrieron como la única manifestación de posible compromiso extrapulmonar.

Todos los enfermos se sujetaron a toracotomía, pero sólo uno sobrevivió más de dos años.

Es de dudarse si la toracotomía es justificada en estos enfermos aunque no se encuentren celdillas malignas en el líquido pleural.

RESUME

L'auteur rapporte 21 cas de cancer bronchique avec épanchement pleural, survenant comme unique manifestation d'une atteinte extrapulmonaire possible. Tous furent soumis à la thoracotomie, mais un seulement survécut plus de deux ans. L'auteur se demande si la thoracotomie est justifiée chez ces malades, même si des cellules malignes ne sont pas mises en évidence dans le liquide pleural.

ZUSAMMENFASSUNG

Bericht über 21 Fälle von bronchogenem Carzinom mit pleuralem Erguss, der als einzige Manifestation möglicher extrapulmonaler Beteiligung auftrat. Es wurden alle Fälle einer Thorakotomie unterzogen, jedoch überlebte nur ein Patient mehr als 2 Jahre. Es wird die Frage gestellt, ob die Thorakotomie bei diesen Patienten gerechtfertigt ist, auch wenn bösartige Zellen in der Pleurafluüssigkeit nicht nachgewiesen werden.

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The Value of Chemotherapy for Active Pulmonary Tuberculosis in Out-patient Clinic

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Introduction

Recent advancement in the treatment of tuberculosis especially chemotherapy has brought a considerable change in the concept of this dreadful disease. Before the era of chemotherapy, rest was considered the most important portion of the treatment of pulmonary tuberculosis, however, since the introduction of effective drugs, the value of rest has apparently decreased. Thus it causes less economic burden for the care of tuberculosis individually as well as nationally. It is particularly significant in those areas where sufficient hospital facilities are not available for all discovered active pulmonary tuberculosis patients. In recognition of this advantage of applying chemotherapy, since late 1954, out-patient clinics have been operated as a control measure for over 800,000 pulmonary tuberculosis patients against 22 million population in Korea. This paper is to report the results of our investigation on the ambulatory chemotherapy for active pulmonary patients for a period of two years at the two largest clinics.

It may be necessary to state clearly that the majority of patients reviewed here continued their normal life during the course of treatment due to economic reasons so that perhaps the results presented here may not be quite comparable to the results obtained in those areas where other necessary measures besides chemotherapy could be adequately provided.

Method of Investigation

Material for the investigation was that of 5,793 patients who received chemotherapy among 7,020 diagnosed active pulmonary tuberculosis patients at Korea's two largest Tuberculosis Clinics of National Tuberculosis Center and Severance Chest Clinic in Seoul from January 1, 1955 to August 31, 1957. The number of patients received chemotherapy over 12 months and 24 months were 1,014 and 276 respectively. This low rate of continuing chemotherapy indicates the difficulties we are facing in the care of tuberculosis and felt the need of strong socio-economic support to these patients to continue their valuable treatment.

Four regimens of chemotherapy have been employed: 1. Streptomycin-isoniazid 254 patients (25 per cent) of total treated patients, 2. PAS-isoniazid 571 patients (58 per cent), 3. Streptomycin-PAS 149 patients (15 per cent), 4. Twenty-eight patients also received triple drug combina-

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TABLE I
CHARACTERISTICS OF 1,014 PATIENTS WITH ACTIVE PULMONARY TUBERCULOSIS AT THE START OF CHEMOTHERAPY

	Number	Per Cent
State of disease		
Minimal	133	13
Moderately advanced	484	48
Far advanced	397	39
Duration of disease		
Less than one year	609	60
One to 5 years	341	34
More than 5 years	64	6
History of Previous Chemotherapy		
None	437	43
0-6 months	389	38
More than 6 months	188	19

tion treatment in consideration of the seriousness of the disease. The isoniazid alone was 12 patients (1 per cent).

There are three important items from the viewpoints of public health on this table: namely, 87 per cent of all patients who have visited clinics showed moderately or far advanced disease and more than a half of the patients received chemotherapy regularly or irregularly before they visited clinics, furthermore, only 1,014 patients actually continued chemotherapy over 12 months out of 5,793 patients who initiated treatment at the clinics.

Result

A. Bacteriologic Results: As Table II shows, in 673 of the total of 1,014 patients sputum culture were positive for tubercle bacilli at the time treatment was begun, and in 252 (37 per cent) were negative on culture following 12 months of chemotherapy, however, reversion in sputum culture was also found in 32 patients (11 per cent), but a little difference in the sputum status was observed at 24 months compared with 12 months results. However, in the group of patients previously untreated showed 49 per cent sputum conversion rate against 25 per cent of previously treated group at 12 months and showed only 41 per cent and 36 per cent respectively at 24 months.

B. Roentgenographic Results: Little difference was observed in the rate of roentgenographic improvement at 12 and 24 months as Table III shows.

In the group of 12 months observation, patients with no previous chemotherapy showed 78 per cent of improvement in comparison with 51 per cent in the group of patients with the history of previous chemotherapy and

TABLE II
BACTERIOLOGIC RESULTS

Culture report at start	Culture report at 12 & 24 months				Per cent converted
	Total	Positive	Negative	No report	
	*				
Positive	673/209	416/129	252/79	5/1	37/38
Negative	281/34	32/6	247/47	2/1	11/11
No report	60/13	5/0	23/7	32/6	

*12 months/24 months

TABLE III

ROENTGENOGRAPHIC CHANGES AT 12 & 24 MONTHS

Stage at start of treatment	Total	Roentgenographic Status at 12 & 24 months					
		Improvement		No change		Deterioration	
		Number	per cent	Number	per cent	Number	per cent
	*						
Minimal	134/17	108/14	81/82	21/2	16/12	5/1	3/6
Mod. Adv.	486/133	399/110	80/83	75/19	15/14	22/41	5/3
Far Adv.	394/126	296/94	71/75	83/21	21/17	15/11	8/8
All Pts.	1,014/276	793/218	78/79	179/42	18/15	42/16	4/6

*12 months/24 months

almost the similar results were observed at 24 months in 82 per cent and 54 per cent respectively among the two groups observed.

C. Final Results: Table IV shows the over all status after 12 and 24 months of chemotherapy, and clinical classification was made by 1955 National Tuberculosis Association Classification and Diagnostic Standards. At the end of 12 months chemotherapy, only 144 patients among 1,014 patients (14 per cent) became inactive, and in general, more favorable changes were observed in the minimal lesions, in the patients with no history of previous chemotherapy and in patients with more recent diseases, that 53 per cent of minimal become inactive but only 13 per cent of moderately advanced, and almost none of the far advanced cases became inactive.

However, following 24 months of chemotherapy, the rate of inactivation in the diseases was much higher as Table IV shows. In all patients, 27 per cent became inactive compared with 14 per cent at 12 months. Especially, in the patients with minimal lesions 71 per cent became inactive. And even more in those patients with moderately or far advanced lesions became inactive 36 per cent and 11 per cent respectively.

It was also found that previous chemotherapy influenced the results markedly that at 12 months 31 per cent of patients with no history of previous chemotherapy became inactive while only 24 per cent of patients with history of previous chemotherapy and the similar findings were also seen at 24 months that 53 per cent and 39 per cent respectively. Thus, the confirmatory results of more favorable changes in the patients with no history of previous chemotherapy was observed.

TABLE IV

FINAL RESULT (CLINICAL DIAGNOSIS) AT 12 AND 24 MONTHS

Stage of start of treatment	Total	Classification at 12 and 24 months			
		Number		Percentage	
		Active	Inactive	Active	Inactive
	*				
Minimal	134/17	63/5	71/12	47/29	53/71
Mod. Adv.	486/133	422/85	64/48	87/64	13/36
Far Adv.	394/126	385/112	9/14	98/89	2/11
All Pts.	1,014/276	870/202	144/74	86/73	14/27

*12 months/24 months

DISCUSSION

There is a world-wide trend to use chemotherapy on unhospitalized or domiciliary tuberculosis patients increasingly as the successful demonstration of value of chemotherapy on these patients. It does not indicate the unnecessity of sanatorium care for the treatment of tuberculosis. Nevertheless, it has lessened the value of rest in the course of treatment of tuberculosis. However, even during the course of chemotherapy, in case of the patients with active clinical symptoms, it is needless to say that a considerable period of strict rest is also needed while it may shorten the period of rest by chemotherapy. The groups of 1,014 patients who received chemotherapy for 12 months or more and 276 patients for 24 months or more among 7,020 patients diagnosed active pulmonary tuberculosis were entirely dependent upon chemotherapy and they could not take proper rest because of socio-economic reasons. The results we have obtained were that 78 per cent at 12 months and 79 at 24 months roentgenologic clearing, and 37 at 12 months and 38 at 24 months in sputum conversion rate from positive to negative. Roentgenologic clearings are referable to the results obtained from sanatorium or hospitalized patients but sputum conversion rate was considerably lower.

Kinoshita of Japan[1] has reported the results of ambulatory chemotherapy that his group observed, 60-70 per cent of maximum sputum conversion rate at six months and roentgenologic clearing was 80-90 per cent at 12 months of chemotherapy, Robinson et al.[2] have reported the results of chemotherapy on nonhospital tuberculosis patients that 56 per cent at 12 months and 58 per cent at 24 months chemotherapy in sputum conversion rate. In comparison with the above mentioned two groups of investigators, our results especially sputum conversion rate is considerably low. It is because of inadequency in proving sufficient nutrition and rest, especially mental rest. In addition the group we have studied included more moderately or far advanced cases than those two groups of investigators. It is an important fact especially from the viewpoint of the public health that 40 per cent of the comparatively severe patients who received chemotherapy for more than 12 months became non-infectious. The differences between the results of chemotherapy at 12 and 24 months in both roentgenological and bacteriological changes were not significant, and they are comparable to the above mentioned two groups of investigators. We believe that unless the patient shows stabilization of active symptoms and signs of pulmonary tuberculosis within 12 months of chemotherapy, continuous chemotherapy will achieve little, and it is especially true to the patients with history of previous chemotherapy. The patients with no previous history of chemotherapy showed 49 per cent of sputum conversion rate against 25 per cent in the patients with history of six months or more previous chemotherapy. It is however agreeable to the other investigators that maximum sputum conversion will be achieved by chemotherapy within the first six months. But the significant bacteriologic improvement will continue to occur until 12 months.

Thus, there will be no argument or objection to administer chemotherapy to all the active pulmonary tuberculosis patients, but, if no satisfactory results are seen, within 12 months of chemotherapy the continuation of the same regimen of chemotherapy will not be significant, and other possible therapeutic measures such as surgical intervention, if applicable, should be considered. For those inoperable cases, combination of drugs is to be changed in accordance with the results of sensitivity test. The patients with the lesion, inoperable or incurable with chemotherapy alone, must be given rehabilitation program with hope of giving the patients psychological release.

SUMMARY

1. The results of chemotherapy at the end of one and two years on 1,014 and 276 patients among 5,793 proved active tuberculosis patients in 7,020 who visited two of Korea's tuberculosis Clinics of National Tuberculosis Center and Severance Chest Clinic during the period between January 1, 1955 and August 31, 1957 are reported.

2. Forty-eight and 39 per cent of total investigated were moderately or far advanced cases respectively.

3. Sputum negative conversion rate was 37 and 38 per cent at 12 and 24 months chemotherapy respectively.

4. Roentgenographic improvement was seen in 75 and 80 per cent at 12 and 24 months respectively.

5. It is believed that adequate bed rest is important in pulmonary tuberculosis patients given chemotherapy on ambulatory basis.

6. In general, more favorable therapeutic effects were observed in the less advanced, more recent, previously untreated cases.

7. There was not much difference between the results obtained at 12 and 24 months chemotherapy. Therefore, at the end 12 months of chemotherapy, a complete evaluation will be necessary.

8. Ambulatory chemotherapy on pulmonary tuberculosis is a proper therapeutic measure, especially in the region where sufficient hospital facilities are not available for all the active pulmonary tuberculosis patients.

RESUMEN

1. Este es un relato de los resultados de la quimioterapia en 1.014 y 276 enfermos, entre un número de 5,793 de tuberculosis activa demonstrada en 7,020 personas que

acudieron a dos grandes clínicas del Centro Nacional de Tuberculosis en Corea, así como en Severance Chest Clinic durante el período de Enero lo. de 1955 y Agosto 31 de 1957.

2. Cuarenta y ocho por ciento y treinta y nueve por ciento respectivamente, fueron moderadamente o muy avanzados.

3. La conversión de los esputos a negativos, fué de 37 por ciento y 38 por ciento a los 12 y 24 meses respectivamente.

4. La mejoría radiológica se observó en 75 por ciento y 80 por ciento a los 14 y 24 meses respectivamente.

5. Se cree que el resposo en cama adecuado, es importante en los enfermos que se les da quimioterapia ambulatoria.

6. En general, se observó más favorable resultado en los menos avanzados, más recientes y no tratados previamente.

7. No hay mucha diferencia entre los resultados obtenidos a los 12 y a los 24 meses. Por tanto, al cabo de los 12 meses se necesita una revaluación completa.

8. La medicación ambulatoria de la tuberculosis es apropiada especialmente en las regiones en que no hay suficientes camas de hospital para todos los enfermos de tuberculosis activa.

RESUME

1. Les auteurs rapportent les résultates de la chimiothérapie à la fin d'une période d'un à deux ans sur 1.014 et 276 malades, parmi 5.973 malades attients de tuberculose évolutive prouvée, sur les 7.020 qui vinrent en consultation aux deux plus importantes cliniques tuberculoses de Korée, du Centre National Tuberculeux et à la Clinique Thoracique Severance entre le Ier Janvier 1955 et le 31 août 1957.

2. 48% et 39% du nombre total des malades examinés étaient respectivement des cas modérément ou très avancés.

3. Le taux de négativation de l'expectoration fut respectivement de 37% et 38% entre 12 et 24 mois de chimiothérapie.

4. Une amélioration radiologique fut constatée dans 75% et 80% des cas après respectivement 12 et 24 mois de traitement.

5. Les auteurs croient qu'un repos au lit approprié est important chez les malades atteints de tuberculose pulmonaire, traités par la chimiothépie administrée d'une façon ambulatoire.

6. En général, les effets thérapeutiques plus favorables furent observés dans les cas les moins avancés, les plus récents, et sans traitment antérieur.

7. Il n'y eut pas beaucoup de différence entre les résultats obtenus après 12 et 24 mois de chimiothérapie. C'est pourquoi à le fin de 12 mois de chimiothérapie, un bilan complet s'avère nécessaire.

8. La chimiothérapie ambulatoire dans la tuberculose pulmonaire est un boyen thérapeutique convenable, particulièrement dans la région où on ne dispose pas de capacités hospitlières sufficantes pour tous les malades atteints de tuberculose pulmonaire évolutive.

ZUSAMMENFASSUNGEN

1. Bericht über die Ergebnisse der Chemotherapie nach einem und nach zwei Jahren bei 1014 und bei 276 Kranken von 5793 nachgewiesenen aktiv-tuberkulösen Kranken unter 7020, die die zwei grössten Koreanischen Tuberkulose-Kliniken des National Tuberculosis Center und der Severance-Thoraxklinik während der Zeit vom 1. 1. 1955 bis 31. 8. 1957 aufsuchten.

2. Bei 48% und 33% aller untersuchten Kranken handelte es sich um mässige, beziehungsweise weit fortgeschrittene Krankheitsformen.

3. Die Sputumkonversionsrate betrug 37% und 38% nach 12 Monaten und nach 24 Monaten Chemotherapie.

4. Röntgenologische Besserung war erkennbar in 75% und in 80% nach 12, bezw. 24 Monaten Behandlung.

5. Es wird die Annahme ausgesprochen, dass adäquate Bettruhe von Wichtigkeit ist für solche Kranken mit Lungentuberkulose, die eine ambulante Chemotherapie erhalten.

6. Im allgemeinen konnte man mehr günsige therapeutische Effekte boebachten bei den weniger fortgeschrittenen, frischeren unbisher behandelten Fällen.

7. Es bestand kein grosser Unterschied in dem Ergebnissen, die nach 12 und nach 24 Monaten Chemotherapie von 12 Monaten eine komplette auswertung notwendig sein.

8. Ambulante Chemotherapie bei Lungentuberkulose ist eine geeignete therapeutische Massnahme, besonders in Gegenden, in denen ausreichende Anstaltsunterbringung für alle aktiven Lungentuberkulöse-Kranken nicht zur Verfügung steht.

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The Superiority of Enzyme Impregnated Paper for Determining Glycosuria in Patients Receiving Antituberculosis Drug Therapy*

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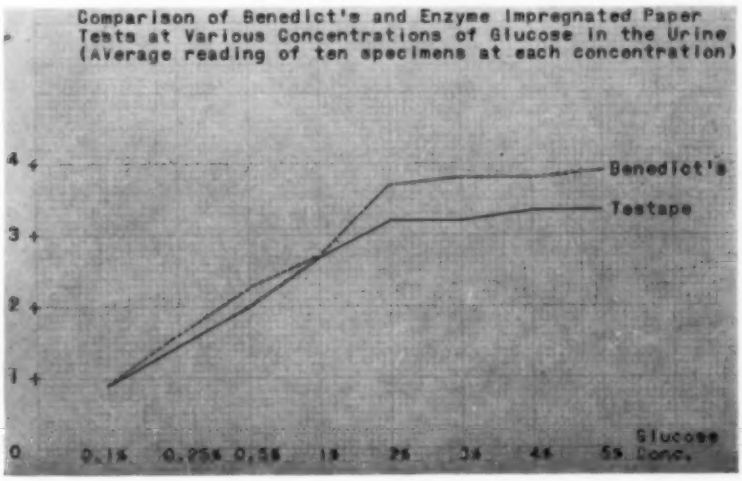
Qualitative and quantitative analysis of the urine for glucose is generally accepted as a useful measure for the detection of diabetics and for the daily follow up of those with proved diabetes as a rough practical estimation of the degree of control of blood sugar levels. In the past the test commonly employed using Benedict's Solution depended on the fact that cupric sulfate was reduced in the presence of glucose in the urine to cuprous oxide, an insoluble yellow or red precipitate. More convenient tablets such as "Clinitest" utilize the same principle of copper reduction. It has been known that reducing substances, other than glucose will at times give a false-positive test in the urine using copper reduction method, but generally these instances were infrequently encountered clinically. In addition there has, in the past, been no simple specific test for urine glucose available, so that to prove by further identification that the reducing substance in the urine was actually glucose involved such procedures as paper chromatography, fermentation tests or the osazone test, none of which is particularly adaptable for bedside use.[1] Recently the development of a testing paper impregnated with the enzyme, glucose-oxidase, has made available a simple specific test for glucose in the urine.* The enzyme, glucose-oxidase, reacts with glucose to form hydrogen peroxide and gluconic acid. The hydrogen peroxide then reacts with peroxidase and orthotolidine, also impregnated in the paper, to form a light green to blue-black color depending on the concentration of glucose present in the urine.

The present study is submitted to call attention to a clinical situation in which the presence of reducing substances in the urine other than glucose is a relatively common occurrence, namely, in patients receiving antituberculosis drug therapy, and the usefulness of the enzyme impregnated test paper under these circumstances as a test for glycosuria. A survey was made on the tuberculosis service of the Providence Veterans Administration Hospital for the incidence of false-positive tests for glucose in the urine using the copper reduction method. Of 40 patients receiving antituberculosis drugs, 30 (75 per cent) were found to have false-positive tests for glycosuria with the copper reduction Benedict's test, varying from trace to two plus. None had false-positive tests with the specific enzyme impregnated paper. Blood sugar determinations in the fasting and postprandial states (11 a.m.) were carried out on each patient, all of which were normal. The results are shown in Table I.

Interference of antituberculosis drugs in the testing of urine for glucose with the copper reduction methods has been noted in other studies.

*From the Medical Service, Veterans Administration Hospital.
*Tes-Tape—Eli Lilly and Company.

Neuberg[2] reported this phenomenon in patients receiving streptomycin. Goldner[3] noted a reducing substance in the urine as the result of PAS administration. Exact identification of the reducing substance in each instance was not carried out but glucose was excluded. It was considered that the reducing substance was due to drug administration, and was one of the breakdown products or the drug itself. In regard to isoniazid both this drug and its principal breakdown product acetyl isonicotinic acid hydrazide are strong reducing agents. That this drug can give false-positive reducing tests for glycosuria was reported by Luntz and Smith.[4] It was their opinion, in addition, that isoniazid produced abnormalities in glucose metabolism with a tendency to hyperglycemia, a point which was not substantiated in the present study. In our survey of 40 patients, all those with false-positive tests for glycosuria were receiving both isoniazid in doses of 300 milligrams daily and PAS in doses of 12 grams daily, except in two instances. One patient was receiving streptomycin one gram twice weekly in addition to the two drugs mentioned, and one was receiving streptomycin alone in doses of 0.5 gram daily (other drugs having been interdicted because of sensitivity reactions). It was not considered advisable to discontinue combined treatment in those with false-positive Benedicts' tests to try to further identify which drug or combination of them was responsible for the false-positive test in each case. It seemed clear from a clinical standpoint that significant numbers of patients receiving these drugs have false-positive copper reduction tests for glycosuria, and this is circumvented by the use of the enzyme impregnated paper. The crucial point in the use of the enzyme paper method then became its reliability in detecting glycosuria when glucose in varying concentrations is actually present in the urine. A comparison of the Benedict's test and the paper enzyme test was then carried out by mixing varying amounts of glucose with sugar-free urine so as to obtain concentrations of 0.1 per cent, 0.25 per cent, 0.5 per cent, 1.0 per cent, 2 per cent, 3 per cent, 4 per cent and 5 per cent. The mixture was allowed to stand one hour. A total of 10 specimens were tested at each concentration



using both Benedict's and the paper enzyme method. The testing was done by technicians following the standard procedure in each test. Those doing the tests were unaware of the actual concentration of glucose in the specimens prior to the test. The average reading at each concentration of glucose by each method is shown in Figure 1. As can be seen, there is a slight tendency to "underread" the paper enzyme test at the higher concentrations of glucose. This is in agreement with the report of Leonards.[5] However, it should be noted that the Benedict's test was not always read as four plus in the higher glucose concentrations. The difficulties in each test concern matching color charts by the eye of the observer. In addition it should be remembered that the amount of glycosuria is at best a rough guide as to be the degree of hyperglycemia. Taking these factors into consideration, it is the opinion of the author that the enzyme impregnated specific test for glucose is superior as a testing material for determination of glycosuria in patients under drug treatment for pulmonary tuberculosis.

SUMMARY

1. False-positive tests for glycosuria using Benedict's test were found in 30 of 40 patients receiving antituberculosis drug therapy with isoniazid, para-aminosalicylic acid and streptomycin, in a range of trace to two plus. .

2. None of the patients had false-positive reaction for glycosuria using a specific enzyme impregnated test paper (Tes-Tape).

3. The use of enzyme impregnated testing paper is recommended for the routine determination of glycosuria in patients receiving the present day commonly used antituberculosis drugs. It appeared sufficiently accurate in detecting true glycosuria when compared with Benedict's reagent in testing urines with known concentrations of glucose.

RESUMEN

1. Se encontraron reacciones positivas falsas de glicosuria usando el reactivo de Benedict, en 30 en 40 enfermos que han recibido drogas antituberculosas con isoniacida, PAS y estreptomicina siendo estos resultados de huellas hasta positivo 2.

2. Ninguno de los enfermos tuvo una reacción positiva falsa cuando se usó una enzima específica en cinta de papel impregnado.

3. El uso de cinta de papel impregnado de enzima se recomienda para la investigación de rutina de la glicosuria en enfermos que usan las drogas antituberculosas actuales. Parece suficientemente exacta para descubrir la verdadera glicosuria en comparación con el reactivo de Benedict al probar orinas con conocidas concentraciones de glucosa.

RESUME

1. Des réponses faussement positives et même extrêmement positives décelant la glycosurie selon la méthode de Benedict, furent découvertes chez 30 malades sur 40 en cours de traitement par les médications antituberculeuses avec isoniazide, P.A.S. et streptomycine.

2. Aucun des malades n'eut de réaction de glycosurie faussement positive lorsqu'on employa un papier-test imprégné d'un enzyme spécifique (Tes-Tape).

3. L'emploi d'un papier-test imprégné d'enzyme est recommandé pour la détermination courante de la glycosurie chez les malades recevant les médications antituberculeuses communément employées de nos jours. Si on le compare au réactif de Bénedict, il semble suffisamment précis pour dépister la vraie glycosurie, lorsqu'on examine des urines contenant des concentrations connues de glucose.

ZUSAMMENFASSUNG

1. Irrige positive Proben zur Glykosorie bei Gebrauch der Benedikt'schen Proben fanden sich bei 30 von 40 Kranken, die eine antituberkulöse Arzneimittelbehandlung erhalten hatten mit INH, PAS und SM, und zwar in Werten von Spuren bis zu 2-fach positiv.

2. Keiner der Kranken hatte eine fälschlich positive Reaktion auf Glykosorie bei Gebrauch von Testpapieren (Tes-Tape), die mit einem spezifischen Enzym imprägniert war.

3. Der Gebrauch von mit Enzym imprägniertem Testpapier wird empfohlen zur routinemässigen Prüfung der Glykosorie bei Kranken, die die gegenwärtig gewöhnlich verwandten antituberkulösen Heilmittel erhalten. Er erscheint ausreichend genau zur Feststellung einer echten Glykosorie im Vergleich mit Benedikt Reagenz bei der Prüfung von Urin mit bekannten Glykosekonzentrationen.

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Broncho-Pulmonary Shunts in Schistosoma Cor Pulmonale

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In a previous communication one of us (H. Z.)[1] expressed the view that in cor pulmonale due to schistosomiasis, there is probably an increased intrathoracic blood volume, and that gross dilatation of the pulmonary artery and its branches often seen in that condition is due in part to the augmented volume of the pulmonary circuit. Since mean pressure measurements in the pulmonary artery do not show direct correlation with the degree of its dilatation in different cases of this disease, intra-pulmonary shunts between the pulmonary artery and the bronchial arteries were suspected to account for rises in pressure secondary to schistosomal obliterative endarteritis.

Pathology

There are two main forms of pulmonary schistosomiasis which are by no means individually separate; a cardiovascular and a parenchymatous, the one often merging into the other. The ova reach the lesser circulation either from the vesical veins in the S. Haematobium or across a portocaval anastomosis in S. Mansoni, the residence of which is confined to the portal tract. Only living ova are capable of exciting a histiocytic and a fibroblastic reaction in and around the arteriole which they are capable of penetrating. They lie in its immediate vicinity causing endarteritis obliterans and the so-called "bilharzial tubercle" which is 0.5-1 mm. in diameter, greyish in colour, firm in consistency and well fixed to its bed. Microscopically it is at first composed of histiocytes and eosinophils and later, lymphocytes and giant cells. Gradually the tubercle is fibrosed and replaced by a nodular scar; parenchymatous lesions being less frequent than the periarterial.

The deposition of the ova and the consequent train of events are patchy at first but the process becomes generalised as more ova reach the lung

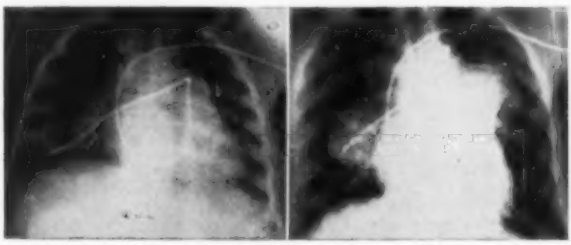

FIGURE 1, Case 1 FIGURE 1, Case 2

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from the prolific schistosoma worms. The deposition favours the perihilar areas and, peripherally, the lower lobe more than the upper while the apices are usually free.

Histologically, the impacted ova in and around the arteriole show a necrotizing arteriolitis with destruction of the media, which heals with obliterative endarteritis. The distinctive histiological feature of the schistosomal pulmonary arteritis is the formation of "angiomatoids." The occluded vessel becomes canalized by new capillaries some of which dilate forming blood spaces lined by endothelium, and in the absence of an intact medial coat this vascularized tissue expands beyond the normal boundaries of the vessel and may reach cavernous proportions (Shaw and Chareeb).[2] There is also a process of obliterative endarteritis in the vasa vasorum of the big vessel. These pathological processes lead to weakening of the arterial coat of the pulmonary vessels which enlarge in the absence of a constant rise of pressure in the right ventricle or in the pulmonary artery. It may be presumed that the new vascularized tissue with the angiomatous cavernous structure is the connection between the pulmonary artery and the bronchial arterial system.

The Clinical Picture

Well developed cases show the typical pattern of hyperactive cor pulmonale with a diastolic over-loading.[3] Indeed at a certain stage the picture may sometimes resemble that of an interatrial septal communication very closely.[4] Thus there is enlargement and hypertrophy of the right ventricle accompanied by a distinct systolic parasternal pulsation in the third and the fourth left intercostal spaces, which may extend to the second space in the event of aneurysmal dilatation of the pulmonary artery. Marked engorgement of the neck veins in the semi-sitting position

DIFFERENT STAGES IN THE EVOLUTION OF SCHISTOSOMA COR PULMONALE

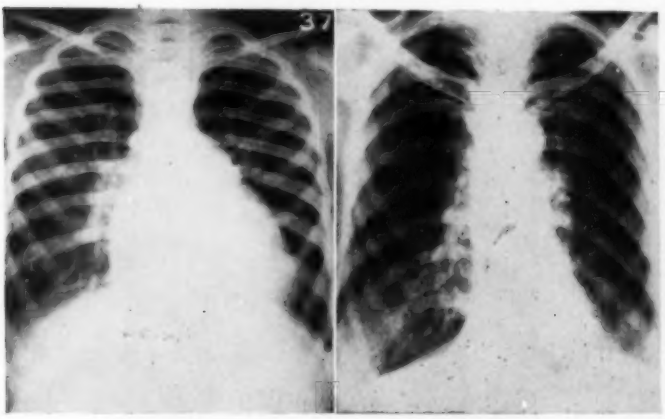

FIGURE 2 FIGURE 3

Figure 2: Parenchymatous involvement with endobronchilitis obliterans and adjacent bronchiolectasis. A picture of honey-comb lung.—*Figure 3:* Early vascular lesion with enlargement of the main trunk of the pulmonary artery.

is common and a prominent wave may be sufficiently vigorous to be seen and felt in pronounced cases. The radiological picture shows apparent increase in the transverse diameter of the heart with a prominent conus arteriosus; in two of our cases a cardiac catheter was seen to lie on the interventricular septum which then almost constituted the left cardiac border, denoting extreme clockwise rotation and gross enlargement of the right ventricle.

There is pronounced enlargement of the pulmonary artery and its branches, the hili stand out like arched bows on either side while the lung fields appear coarsely vascularized and "plethoric."

The electrocardiogram shows signs of right ventricular hypertrophy, "strain" and diastolic loading.[3] A prominent R wave in V_1 through V_3,

FIGURE 4

FIGURE 5

Figure 4: Beginning aneurysmal dilatation of the pulmonary artery and its branches with radiating vascular shadows.—*Figure 5:* Further stage of isolated aneurysm of the main trunk.—*Figure 6:* Aneurysm of the pulmonary artery trunk and its branches with evident parenchymatous lesions.

FIGURE 6

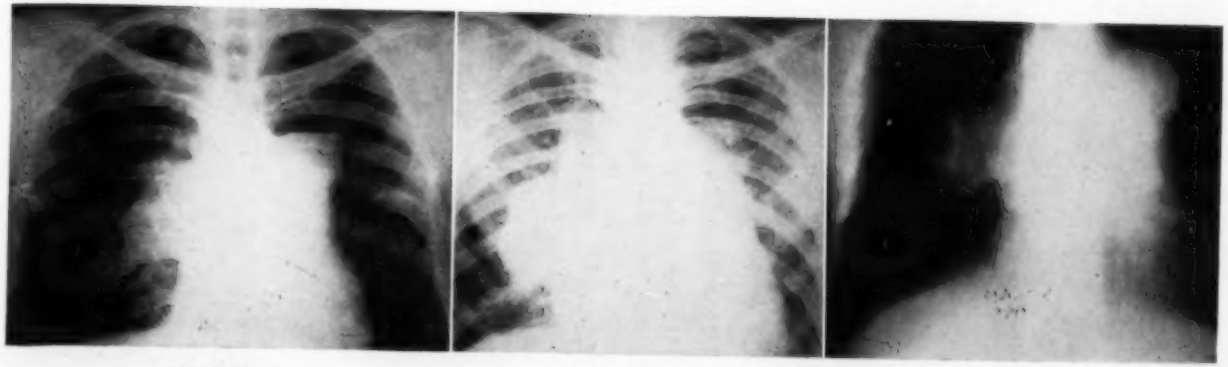

FIGURE 7 FIGURE 8 FIGURE 9

Figures 7 and 8: Marked aneurysmal dilatation of all the main branches of the pulmonary artery with enlargement of the right ventricle.—*Figure 9:* Tomography of Case 5.

TABLE I

No.	Name	Age	Haemo-globin	Blood Volume Per Cent	Plasma Volume	Electrocardiogram
1	M. I.	12	79	3598 c.c.	2267 c.c.	Right ventricular hypertrophy and strain
2	M. M. Z.	40	82	5636 c.c.	3316 c.c.	Right ventricular strain
3	A. A. S.	40	76	5436 c.c.	2290 c.c.	Right ventricular hypertrophy and strain
4	A. E. S.	36	93	.....	.....	Right bundle branch block
5	M. A. S.	12	93	.....	.....	Right ventricular hypertrophy

deep S wave in V_6-V_7, depression of ST segment and inverted T wave in V_1-V_3 or more and incomplete R.B.B.B. A Q wave in the right precordial leads may also be present while right axis deviation is usual.

Material and Methods

In an attempt to establish the presence of shunts between the pulmonary artery branches and the bronchial arterial system during life, five cases of well developed cardiopulmonary schistosomiasis with gross dilatation of the pulmonary artery and its branches were investigated. All were males who had hepatosplenomegaly and schistosoma ova in the urine or stools or both.

Cardiac catheterization was done and the oxygen content was determined by the Van Slyke method at three levels in the course of the pulmonary artery: (1) in the pulmonary artery main trunk, (2) midway in the dilated pulmonary artery branch, and (3) in the prewedged position of the catheter.

The cardiac output was determined according to the Fick principle. The blood volume was determined by the Evans blue method (T 1824). The

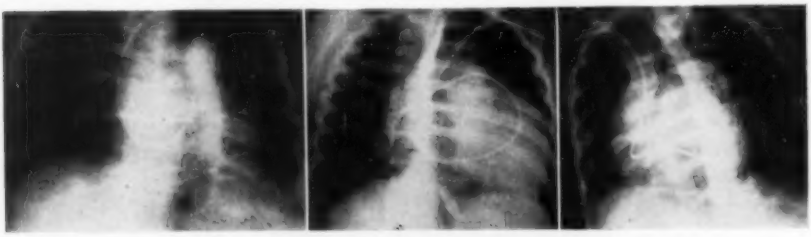

FIGURE 10 FIGURE 11 FIGURE 12

Figure 10: Localised angiopneumography of case 4.—*Figure 11:* Catheter in right oblique position.—*Figure 12:* Catheter in left oblique position showing extent of enlargement of the right ventricle.

TABLE II
PRESSURES AND OXYGEN CONTENT AT DIFFERENT LEVELS IN THE PULMONARY ARTERY

No.	Pulmonary Artery Trunk		Right Pulmonary Artery		Prewedged Position		Femoral Artery	Degree of shunt Per Cent
	Pressure (mm.Hg.)	Oxygen (Vol.) Per Cent	Pressure (mm.Hg.)	Oxygen (Vol.) Per Cent	Pressure (mm.Hg.)	Oxygen (Vol.) Per Cent	Oxygen (Vol.) Per Cent	
1	65	7.6	63	9.1	25	9.1	13.4	34.8
2	72	10.2	70	12.9	70	13.6	15.5	92
3	62	13.4	—	14.1	—	14.9	18.2	30
4	60	12.9	—	13.6	—	14.3	17.7	41
5	55	9.6	—	9.6	35	15.6	—	—

magnitude of the shunt was calculated using Cournand's Formula:[5]

$$Y_s = Q_s \frac{Cpa - Crv}{Cao - Cpa}$$

Where:
Y_s = Shunt of blood.
Q_s = Systemic blood flow.
Cpa = Oxygen concentration in pulmonary artery.
Crv = Oxygen concentration in right ventricle.
Cao = Oxygen concentration in the aorta.

ANALYSIS OF THE RESULTS

Case 1: In this case it will be seen that the oxygen content of the samples removed from the right pulmonary artery and from the prewedged site is the same and that it is higher than that obtained from the main trunk by 1.5 volumes per cent. Since the femoral artery had an oxygen content of 13.4 volumes per cent (from associated anemia); and since the pulmonary artery blood could not be arterialized except from the arterial system (the samples being too far away from the pulmonary bed), the existence of a left to right shunt is presumed. It is also seen that the degree of this shunt equals a little more than one third of the pulmonary blood flow. This amount, which is short-circuited back to the left side of the heart, explains the left ventricular hypertrophy which is sometimes noticed in cases of schistosoma cor pulmonale without accountable reason.

Case 2: In this case the pressure in the pulmonary artery is similar to Case 1. Nevertheless, the size of the pulmonary artery is indeed outstanding. If the oxygen content of the pulmonary artery branch is accepted as illustrative of a homogeneous mixture, then the degree of the shunt in this case is almost equal to the pulmonary artery blood flow. The estimated figure from the prewedged position is probably

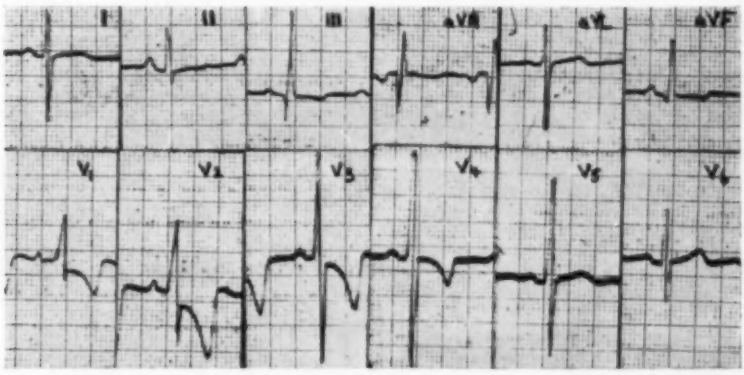

FIGURE 13: E.C.G. showing right bundle branch block and right ventricular "strain."

too high (table II) and suggests that the catheter was facing the main stream of the shunt. Thus is explained the discrepancy in the size of the pulmonary artery between this case and the previous one although both had equal pressures.

Case 5: This case is reported in some detail because of its interesting features. M.A.S. is a 12 years old boy whose main complaint was cough, expectoration and attacks of bronchial asthma. The patient was cyanosed and had wheezes all over the chest. The apex beat was diffuse in the sixth space, just outside the midclavicular line. There was gallop rhythm and a soft apical systolic murmur. There was left parasternal lift, dullness in the second left space, harsh systolic pulmonary murmur and a reduplicated pulmonary second sound. He had schistosomal hepatosplenomegaly and slight digital clubbing. Radioscopy revealed increased transverse diameter of the heart, prominent conus and hilar danse. Radiography showed a honey-combed lung.

The shunt in this case was demonstrated in the prewedged position only. The communication therefore seems to be located peripherally rather than centrally. This may account for the predominant lung symptoms of cough and repeated attacks of asthma from associated bronchiolitis. The prewedged position reflected the high pressure of 30 mm. Hg. The pulmonary artery did not show the gross dilatation seen in the previously described cases possibly due to the young age of the patient or to a peripheral localization of the pathological process.

DISCUSSION

The above cases were picked at random, the sole criteria being the presence of schistosomal cor pulmonale with prominent or gross dilatation of the pulmonary artery; congenital heart disease being excluded by cardiac catheterization. They constitute the first five cases of a series under investigation. Each case demonstrated a significant rise in the oxygen content at different levels in the course of the pulmonary artery from its origin to the peripheray as it crosses the lung. Such oxygen gain can only take place through the bronchial arteries. A communication of this sort is known to exist in various lung and heart disease,[6-15] i.e. chronic degenerative lung disease (emphysema), fibrosis of the lung, atelectasis, cystic lung disease, chronic pulmonary tuberculosis and in pulmonary infarcts; and in congenital heart conditions characterized by pulmonary oligaemia, i.e. pulmonary stenosis, Fallot's tetralogy, hypoplastic right ventricle and persistent truncus arteriosus. In spite of the raised pressure in the pulmonary arteries in advanced emphysematous cor pulmonale, there is usually no associated prominent dilatation of the pulmonary artery except in older subjects in whom the elastic tissue has deteriorated from progressive atherosclerosis and repeated infections. The lung is ischemic and the peripheral pulmonary arterioles are reduced in size and offer a high resistance. In mitral stenosis any dilatation of the pulmonary artery or hypertrophy of the right ventricle reflects the presence of a high pulmonary arteriolar resistance. The engorgement of the lung is limited to the venous side and stops short of the arterioles. In spite of very high mean pressures in the pulmonary artery in mitral stenosis, such diffuse aneurysmal dilatations are not seen except in Lutembacher's syndrome or post-occlusive infarcts. Any enlargement is only moderate and practically limited to the proximal parts; no gross dilatation of the distal branches as demonstrated by angiography ever takes place as in our cases. On the contrary the peripheral vessels are reduced in size.[16] Dilatation of the pulmonary artery from Eisenmenger's complex, interatrial septal defect and patent ductus arteriosus are congenital conditions which may show gross dilatation of the pulmonary artery. The first two are examples of manifestations of diastolic overloading[17] and pulmonary artery "plethora." Pressure readings in that vessel may be only moderately raised in spite of the presence of cor pulmonale and a large pulmonary artery.[17]

Schistosoma cor pulmonale is perhaps unique in that it is an acquired parasitic disease with an assumed broncho-pulmonary shunts which, haemodynamically, resembles congenital heart conditions with left to right shunt. Thus there is gross widening of the pulmonary artery and its peripheral branches with apparent "plethora" in the presence of moderate or marked, pulmonary hypertension and a picture of advanced cor pulmonale with diastolic loading and sometimes a hyperkinetic circulation. Though a hyperkinetic circulation from general causes, e.g. severe anaemia, thyrotoxicosis or polycythemia rubra, etc. may produce some dilatation in the pulmonary artery, it does not approach in degree that seen in our cases.

It is difficult to conjecture at which time in the life history of the disease such presumed shunts take place. Advanced cases with gross and aneurysmal dilatation of the pulmonary artery have been chosen purposely in an attempt to establish first the presence of a shunt, but it seems logical to assume that these broncho-pulmonary communications develop hand in hand with the formation of angiomatoid vascular network.

SUMMARY

1. Schistosomiasis is an endemic disease in Egypt.

2. Enlargement of the pulmonary trunk and its main branches is sometimes found along with a picture of diastolic loading of the right ventricle and cor pulmonale.

3. A series of cases have been investigated by means of cardiac catheterization and the oxygen saturation was found to increase in a significant degree as the catheter proceeds from the pulmonary trunk towards the periphery along the course of an enlarged pulmonary artery. A left to right shunt is therefore presumed across the vascular net of the broncho-pulmonary arteries.

4. The seat of anastomosis is believed to be a development of communication between the schistosomal "angeiomatoid" formation and the broncho-pulmonary arteries.

5. Schistosomal "Cor Pulmonale" is therefore an acquired parasitic disease that illustrates in its features manifestations usually found in congenital heart disease.

RESUMEN

1. La esquistosomiasis es una enfermedad endémica en Egipto.

2. El crecimiento del tronco de la pulmonar y de sus ramas-principales se encuentra algunas veces, con un cuadro de sobrecarga diastólica del ventrículo derecho y cor pulmonale.

3. Por medio de la cateterización cardiaca se ha estudiado una serie de casos y se encontró que la saturación de oxígeno está aumentada en un grado significativo cuando el cateter avanza desde el tronco pulmonar hacia la periferia a lo largo de una arteria pulmonar ensanchada. Se presume que hay una intercomunicación de izquierda a derecha a través de la red vascular de las arterias broncopulmonares.

4. El lugar de las anastomosis se cree que sea por un desarrollo de comunicación entre la formación esquiatosómica "angiomatoide" y las arterias broncopulmonares.

5. El "cor pulmonale" esquistosómico es por tanto una enfermedad adquirida, parasitaria, que ilustra por sus características las manifestaciones habitualmente encontradas en las enfermedades congénitas del corazón.

RESUME

1. La schistosomiase est une affection endémique en Egypte.

2. L'élargissement des vaisseaux pulmonaires et de leurs branches principales existe quelquefois associé à une surcharge diastolique du ventricule droit, et à un coeur pulmonaire.

3. L'auteur a examiné une série de cas au moyen du cathétérisme cardiaque et a trouvé que la saturation oxygénée augmentait dans une proportion notable lorsque le cathéter passe du tronc de l'artère pulmonaire vers la périphérie le long d'une artère pulmonaire élargie. On peut alors soupçonner un shunt de gauche à droite à travers le lit vasculaire des artères pulmonaires.

4. L'auteur pense que le siège de l'anastomose est l'augmentation de la communication entre la formation "angiomateuse" due à la schistosomiase et les artères pulmonaires

5. Le "coeur pulmonaire" de la schistosomiase est aussi une affection parasitaire acquise qui présente les symptômes des manifestations appartenant habituellement aux maladies cardiaques congénitales.

ZUSAMMENFASSUNG

1. Die Schistosomiase ist eine in Agypten endemische Krankheit.

2. Mitunter findet man eine Vergrösserung des conus pulmonalis und seiner Hauptverzweigungen zusammen mit einem Bild diastolischer Überlastung des rechten Ventrikels und cor pulmonale.

3. Es wurde eine Anzahl von Fällen untersucht mit Hilfe der Herzkatheterisierung, und es fand sich eine Zunahme der Sauerstoffsättigung in bertächtlichem Grade in dem Masse wie der Katheter vorrückt vom conus pulmonalis zur Peripherie entlang dem Verlauf einer erweiterten Lungenarterie. Es wird deshalb ein Links-Rechts-Shunt angenommen auf dem Wege über das Gefässnetz der Art. bronchiales.

4. Vom Sitz der Anastomose wird angenommen, dass er sich entwickelt aus eine Kommunikation zwischen der durch die Schistosomiasis bedingten "angiomatoiden" Formation und dem Bronchialarterien.

5. Das durch die Schistosomiasis bedingte "cor pulmonale" stellt daher eine erworbene parasitäre Erkrankung dar, die in ihrem Ablauf Krankheitserscheinungen veranschaulicht, die gewöhnlich bei angeborenen Herzkrankheiten zu finden sind.

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SECTION ON CARDIOVASCULAR DISEASES

The Use of Extracorporeal Circulation in Cardiac Surgery*

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Extracorporeal circulation is now a well-established method which permits the surgical correction of intracardiac defects. There are many different ways to establish cardiac bypass,[1-4] and certainly all presently existing technics will be greatly modified and simplified in the coming years. Yet all would agree that the use of this surgical tool has greatly advanced the surgery of heart disease and will continue to do so.

With methods becoming better standardized and the basic technics more firmly grounded, attention should be directed more closely to the selection of patients for operation than it has been heretofore. The purpose of this paper is to detail our criteria for this selection, following a brief review of the method of extracorporeal circulation in use at our institution and a summary of our surgical experience.

Method of Extracorporeal Circulation

We believe that there are certain basic requirements which must be fulfilled by a satisfactory apparatus for extracorporeal circulation.

The blood should be completely oxygenated without the production of air embolism. Oxygen tension should range between 100 and 300 mm. of mercury, and carbon dioxide tension between 30 and 40 mm. of mercury. Flows should approximate those in effect prior to perfusion, usually varying between 2 and 2.4 liters per minute per square meter. When flows of this amount are in effect, the venous saturation remains in the neighborhood of 70 per cent, the patient's venous pressure varies from 5 to 15 mm. of mercury, and the mean arterial pressure is maintained in the neighborhood of 70 mm. of mercury. Normal body temperature should be maintained and total buffer base and pH should not change significantly. The volume of blood should remain stable, and the pumping apparatus must not traumatize the blood.

We believe that all of these requirements are fulfilled by the modified Gibbon-type vertical-screen oxygenator which has now been in clinical use at our institution for more than 3 years.[5]

Mortality with Open-Heart Operations

During the period from March, 1955 to June, 1958, 440 operations have been performed with employment of extracorporeal circulation. The overall mortality has been in the neighborhood of 25 per cent (table). Obviously the mortality varies considerably, depending on the nature of the defect and the presence of complicating conditions. In the initial group of 20

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cases of ventricular septal defect with pulmonary hypertension reported from the Mayo Clinic, the operative mortality was 20 per cent.[6] The operations in these cases were performed in 1955. In the year 1957 the operative mortality in 70 cases was 12 per cent. This is considered a reasonable figure, since most of these patients had severe elevation of pulmonary-artery pressure.

The tetralogy of Fallot, on the other hand, presents a complicated surgical problem. Among the patients operated on since 1955, the hospital mortality has been 24 per cent.[7] In the most recent 25 cases of this series, there have been 4 deaths, an operative mortality of 16 per cent, and this probably represents more accurately the rate now to be expected from open intracardiac repair of the tetralogy of Fallot.

The hospital mortality rate for atrial septal defect and for pulmonic stenosis has been less than 10 per cent,[8] and there have been no fatalities among the patients undergoing mitral annuloplasty for mitral insufficiency.[9]

Selection of Patients for Operation

The use of extracorporeal circulation should be restricted to patients with defects that cannot be safely and satisfactorily corrected by any other means. With this concept as a basis for selection of patients for operation, it is not surprising that ventricular septal defect and tetralogy of Fallot comprise together more than half of the defects operated upon. There is no other method by which a ventricular septal defect may be closed. Although the palliative procedures introduced by Blalock, Potts, and Brock for the treatment of tetralogy of Fallot were brilliantly conceived and did much to help individuals suffering from this disease, they did not effect complete anatomic correction of the malformation. This can be accomplished only by open-heart repair.

Closure of uncomplicated atrial septal defects by the atrial-well method of Gross has been accompanied in our experience by an operative mortality of less than 2 per cent.[10] Because of this low mortality and because of the excellence of the results, extracorporeal circulation is not used routinely in these cases. Open-heart repair is restricted to those cases with com-

TABLE I
EXTRACORPOREAL CIRCULATION FOR CARDIAC SURGERY

Malformation	Cases
Ventricular septal defect	186
Tetralogy of Fallot	83
Common atrioventricular canal	37
Atrial septal defect	35
Pulmonary stenosis	31
Congenital aortic stenosis	17
Total anomalous pulmonary venous connection	10
Mitral insufficiency	6
Origin of both great arteries from right ventricle	6
Single ventricle	5
Common atrium	5
Ruptured aneurysm of sinus of Valsalva	3
Atrial tumor	2
Mitral stenosis	1
Combined subvalvular aortic and pulmonary stenosis	1
Aneurysm of ascending aorta	1
Miscellaneous	11
Total	440

plicated associated anomalous pulmonary venous connection[11] and those with severe pulmonary hypertension and right ventricular failure, as evidenced by elevation of right atrial pressure, hepatomegaly, and peripheral edema.

Except in the very young patient, it has been our experience that almost invariably significant valvular pulmonic stenosis is complicated by a zone of infundibular obstruction requiring excision. Therefore hypothermia rarely is used in operations in these cases. Extracorporeal circulation is preferred, for this method provides sufficient time for complete relief of infundibular narrowing.

The grossly deformed, calcified, and immobile valve seen in patients with acquired aortic stenosis presents a problem most difficult to overcome. Even under direct vision, the operation is at best a palliative one. For this reason we have used extracorporeal circulation only if the aortic stenosis was congenital. The occasional finding of subvalvular stenosis in these patients makes this approach desirable.

Although one instance of mitral stenosis required reoperation with extracorporeal circulation, the classic closed method of mitral commissurotomy is preferred in these cases. Continued use of this procedure is justified by the satisfactory palliation at low risk that this procedure affords the vast majority of patients so treated.[12] Severely calcified valves which are also incompetent pose a serious problem which may require development of a suitable prosthetic valve.

Hemodynamic Consideration in Left-to-Right Shunts

There remains considerable confusion in the minds of most of us concerning the hemodynamic situation in the presence of a communication between the systemic and pulmonary circulations. In particular, there is uncertainty as to how changes in such hemodynamics may affect the risk of operative closure of this communication.

Communications of this type, of course, include patent ductus arteriosus, aortic-pulmonary window, atrial septal defect, ventricular septal defect, and common atrioventricular canal. Since more than half of the patients operated on with extracorporeal circulation underwent correction of one or another of the three defects last mentioned, it is important to review again certain basic aspects of this problem.

In the absence of a communication between the two systems, pulmonary and systemic flows normally are equal. The pulmonary pressure is about one fourth of the systemic pressure and the pulmonary resistance is lower than the systemic resistance. It follows naturally that when a communication exists between the two systems, blood flows from left to right—that is to say, from the systemic to the pulmonary system.

A left-to-right shunt may or may not be accompanied by elevation of the pulmonary-artery pressure. Pressure, it will be recalled, is dependent on flow and resistance. Thus pulmonary hypertension can be due in major part to a large pulmonary flow or it can be due in major part to increased pulmonary resistance. Since the purpose of operative closure of an abnormal communication between the systemic and pulmonary circulations is to reduce pulmonary flow, the presence of an increased pulmonary flow must be determined preoperatively in order to justify operation.

In most instances pulmonary hypertension is at first a reflection of increase in pulmonary flow which is due to a large left-to-right shunt. In time changes develop in the smaller pulmonary vessels, leading to an elevation of resistance in the pulmonary circuit and a reduction in pulmonary flow. This is then accompanied by a right-to-left shunt—blood passing from pulmonary to systemic circulation. The shunt becomes bidirectional. When pulmonary resistance exceeds systemic resistance, pulmonary flow will be subnormal and right-to-left shunting will predominate.

Obviously in this latter condition closure of the communication will not lower pulmonary flow; if anything, it will increase it. Of patients with severe pulmonary hypertension and a shunt which has become predominantly right-to-left, none, so far as we know, have survived long after complete and proven repair of their defect.

In brief, closure of a defect between the two systems is well tolerated when the shunt is entirely left-to-right; and an elevated pulmonary-artery pressure, if present, can be expected to fall after closure. In the presence of a bidirectional shunt, operation may be expected to lower pulmonary-artery pressure—although at some increase of risk—provided the left-to-right shunting predominates. When the shunt is predominantly right-to-left (pulmonary resistance exceeding systemic resistance) surgical correction is not safe in the present stage of our knowledge.

Ventricular Septal Defect

How can this information be of help in selecting for operation patients with ventricular septal defect? Those patients whose hearts are normal in size and whose electrocardiographic findings are virtually within normal limits are not considered by us as candidates for operation at the present time. In these cases pulmonary-artery pressure is normal and left-to-right shunts are relatively small.

Operation should be considered when pulmonary hypertension is present. Almost all of our patients have had pulmonary hypertension and in three fourths of them the aortic and pulmonary-artery pressures were comparable. It should be emphasized that neither the level of the pulmonary-artery pressure nor its relationship to the level of aortic pressure is a matter of chief importance. Rather it is the degree of pulmonary resistance and the effect of this resistance on the direction and magnitude of the shunt and thus upon pulmonary blood flow that are of primary significance.

Estimation of the magnitude of pulmonary blood flow and deduction from it regarding that state of the pulmonary vasculature and pulmonary resistance become of chief concern in the consideration of whether to operate on a patient with a ventricular septal defect and pulmonary hypertension. Cardiac catheterization is the most direct way of measuring these variables. We have come to rely heavily, however, on the clinical findings which bear upon these matters. Largely on the basis of observations by Dr. J. W. DuShane, certain clinical criteria have been formed which now make it but rarely necessary to catheterize a patient with a ventricular septal defect in order to determine operability.

These factors indicating operability include overactivity of the heart,

prominent pulsation of the hilar vessels and hyperemia of the lung fields as seen by roentgenoscopy and roentgenography, and left ventricular diastolic overload indicated by the ECG.

Common Atrioventricular Canal

Similar clinical criteria should be applied in selecting for operation patients with common atrioventricular canal. The indication of left ventricular overload on the electrocardiogram is a less helpful prognostic sign in these cases because of the associated mitral insufficiency which is almost invariably present.

This defect is a complicated one and may present itself in a partial or a complete form. Both forms are characterized by a defect in the lower portion of the atrial septum and a cleft in the septal leaflet of the mitral valve. The complete form, in addition, has a cleft tricuspid valve and a communication between the two ventricles. Repair of the partial form is readily accomplished with use of extracorporeal circulation, and the mortality rate is low. A high mortality rate accompanies attempted repair of the complete form because of the complex nature of the defect and the severity of the pulmonary-artery changes that so often are present.

Tetralogy of Fallot

There remains considerable difference of opinion regarding the proper surgical management of patients with tetralogy of Fallot. The clinical results in patients surviving complete repair of the defect are so gratifying that in spite of the operative risk, which presently is in the neighborhood of 16 per cent, open repair of the defect is now advised at the Mayo Clinic for all patients with this malformation.

The technical aspects of the operative management of these patients are of great importance. Relief of the pulmonary stenosis is essential, and various maneuvers have been employed to achieve this. Complete relief of the pulmonary-artery obstruction is not always possible, and the operative mortality among such patients is high.

Acquired Heart Disease

Extracorporeal circulation has a part also in the management of patients with acquired heart disease. We have been gratified by the clinical response to mitral annuloplasty of patients with severe, relatively pure mitral insufficiency. Six such patients have now undergone operation without mortality. A marked decrease in heart size and return of hemodynamic factors toward normal have been noted.[9]

Intracardiac tumors are amenable to surgical removal with extracorporeal circulation.[13] We have operated successfully in two such cases. In one of them a huge myxoma was removed from the right atrium of a 48-year-old man suffering from marked elevation of venous pressure, hepatomegaly, ascites, and peripheral edema. Postoperatively, all symptoms were relieved. In the other, a myxoma was successfully removed from the left atrium of a 45-year-old woman.

SUMMARY

This brief review serves to emphasize the ever-broadening scope of cardiac surgery brought about in great measure by the proper application of extracorporeal circulation. Now that the technics have been improved and standardized, proper selection of patients will determine to a great extent the success or failure of this method of treatment.

More than half of the patients we have operated on have had either a ventricular septal defect or the tetralogy of Fallot. We have discussed criteria for selection of patients with these and other conditions.

RESUMEN

Esta revisión breve sirve para destacar cuán amplio y creciente es el campo de la cirugía cardiaca, debido en gran parte al uso de la circulación extracorpórea. Ahora que la técnica ha sido mejorada y estandarizada, la selección adecuada de los enformos en gran medida determinará el éxito del procedimento, o bien su fracaso. En más de la mitad de los enfermos en quienes hemos operado, he existido ya sea un defecto spetal o una tetralogía de Fallot. Hemos analizado el criterio para la selección de los enfermos con ésta y otras condiciones patológicas.

RESUME

Cette rapide revue tend à mettre l'accent sur le domaine toujours plus étendu de la chirurgie cardiaque amenée à un grand développement par l'application appropriée de la circulation extra-corporelle. Maintenant que les techniques ont été améliorées et standardisées, un choix judicieux des malades déterminera jusqu'à quel degré on peut attendre le succès ou l'échec de cette méthode de traitement. Plus de la moité des malades que les auteurs ont opérés ont eu une altération de la paroi ventriculaire ou une tétralogie de Fallot. Ils discutent les critères de sélection des malades atteints de l'une ou de l'autre de ces affections.

ZUSAMMENFASSUNG

Diese kurze Übersicht dient der Hervorhebung des sich immer mehr vergrössernden Gebietes der Herzchirurgie, die im grossen Masse durch die zweckmässige Anwendung des extracorpuralen Kreislaufes zu Wege gebracht wurde.

Nachdem nun die Tecknik verbessert und vereinheitlicht worden ist, wird eine entsprechende Auswahl von Patienten bis zu einen erheblichen Grad Erfolg oder Misserfolg dieser Behandlungsmethode bestimmen. Mehr als die Hälfte der von uns operierten Kranken hatten entweder einen Kammerscheidewanddefekt oder litten an Fallot'schen Tetralogie. Wir besprachen die Kriterien zur Auswahl von Kranken mit diesen und anderen Befunden.

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Left Ventricular Hypertrophy Syndrome in Infancy

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Cardiac hypertrophy in infancy has been the subject of considerable interest for many years. An increasing number of reports have appeared in the literature describing diverse cardiac lesions in infancy, which nevertheless have similar clinical manifestations. Rosenbaum et al. incorporated this group of diseases under the heading "Primary Myocardial Disease in Infancy and Childhood."[1] Since most of these lesions are not of primary myocardial origin and since they produce left ventricular hypertrophy as the predominant anatomic finding, we offer "Left Ventricular Hypertrophy Syndrome" as a more descriptive title.

The Left Ventricular Hypertrophy Syndrome in infancy is characterized by; (1) cardiac enlargement—predominantly of the left ventricle; (2) absence of significant heart murmurs; (3) absence of central cyanosis; (4) electrocardiographic findings which are either normal or indicative of myocardial damage or of left ventricular hypertrophy; (5) at times, symptoms and signs of cardiac failure.

The lesions associated with this syndrome are conveniently divided into those in which the predominant abnormality is endocardial, as in primary endocardial fibroelastosis; those in which the myocardium is primarily involved and a third group in which there is predominant alteration in function of the coronary arteries.

A number of rather common congenital malformations producing left ventricular hypertrophy in the absence of cyanosis are seen in infancy. These are usually accompanied by significant murmurs and, by definition, are excluded from the syndrome under discussion. They include patent ductus arteriosus, ventricular septal defect, aortic or subaortic stenosis as well as coarctation of the aorta.

In a characteristic instance of the left ventricular hypertrophy syndrome, the history is that of a previously healthy baby who has begun to eat poorly, and to show signs of restlessness and fatigue. Episodes of apparent pain may be noted. Restlessness increases and is often followed by respiratory distress. On examination, dyspnea, tachycardia, enlargement of the heart and, in some instances, gallop rhythm and poor heart sounds are noted. Hepatomegaly is often present due to associated cardiac failure. Cyanosis, if present, is usually transient or terminal. Heart murmurs are conspicuously absent or, if present, consist of soft, inconsequential, apical murmurs. Usually the lungs are clear but evidence of pulmonary infection or signs of atelectasis produced by cardiac enlargement may be present. Peripheral edema is uncommon except as a late manifestation. Radiologic examination reveals considerable cardiac enlargement, the silhouette often being globular in shape; occasionally the standard criteria for left ventricular enlargement are satisfied. The electrocardiogram may be diagnostic of left ventricular hypertrophy or reveal ST or T wave abnormalities indicative of myocardial anoxia or damage.

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We shall discuss the lesions resulting in the left ventricular hypertrophy syndrome as defined, describing their characteristics, differential diagnosis and treatment.

I. *Primary Endocardial Disease*

a. *Primary Endocardial Fibroelastosis* is the most common cause of the left ventricular hypertrophy syndrome in infancy. Kelly and Anderson[2a] collected 79 cases from the literature and added 17 from the files of the Babies Hospital. It is apparent that a larger number of cases have never been reported. Many were formerly classified as idiopathic cardiac hypertrophy of infancy, while in others the cause of death may have been overlooked completely. Kugel and Stoloff[3] were among the first to recognize the significance of endocardial thickening in patients described as having idiopathic cardiac hypertrophy. Andersen and Kelly[2b] emphasized the importance of separating cases of endocardial fibroelastosis into two groups: those without associated cardiac malformations (primary endocardial fibroelastosis) and those associated with congenital malformations in which the endocardial thickening is secondary to hemodynamic changes related to the cardiac malformation. The latter group have been excluded from this discussion as they are not representative of the left ventricular hypertrophy syndrome.

The cause of primary endocardial fibroelastosis is not well understood. Gross[4] was one of the first to point out that there is no evidence of an inflammatory process. He felt that simple hyperplasia of the endocardial fibroelastic tissue best explained the condition, and that it was a developmental defect rather than an inflammatory process. Others[5] have supported this interpretation. The concept that endocardial anoxia may be the stimulus for the production of endocardial fibroelastosis has been suggested by several authors. Thomas et al.[6] indicate that endocardial fibroelastosis associated with other cardiac malformations is confined to patients in whom a clear-cut cause for endocardial anoxia is demonstrated. Craig[7] states that the myocardial degeneration and fibrosis so frequently encountered in the subendocardium is the result of such anoxia. Johnson[8] suggests that, in the primary variety, endocardial anoxia in the left heart may be present in utero due to either delayed opening of the septum primum or early closure of the foramen ovale. The possibility that this is a developmental anomaly has been suggested by the familial incidence in reported cases such as in siblings and multiple pregnancies.[2, 7, 10, 11] In only an occasional case has a specific prenatal maternal illness been present.[9] Assuming that the original cause is either endocardial anoxia or a developmental defect, Weinberg and Himmelfarb[10] propose that the thickened endocardium may prevent adequate nourishment of the myocardium. Drainage of the arterioluminal vessels into the ventricle is obstructed so that partial stasis occurs in intramyocardial capillaries. This results in myocardial anoxia and subsequent myocardial failure. Kelly and Andersen[2a] suggest a possible congenital familial metabolic defect resulting in myocardial weakness with endocardial fibrosis as a secondary phenomenon. They indicate that investigations directed towards a deficiency of some enzyme involved in myocardial metabolism may be a profitable approach to the problem.

The clinical findings in primary endocardial fibroelastosis are similar to those described for the entire left ventricular hypertrophy syndrome. Significant heart murmurs are absent in about 80% of all cases.[12] Cardiac hypertrophy is demonstrable by physical and roentgen examinations. The electrocardiogram reveals no pathognomonic features which distinguish this entity from the other lesions of the left ventricular hypertrophy syndrome. Standard leads in the electrocardiogram often reveal evidence of nonspecific myocardial anoxia or damage with T wave flattening or inversion or, less often, with ST segment deviation. Many of the precordial tracings available in the literature indicate the presence of left ventricular hypertrophy.[13] Deep Q waves with marked ST segment deviation are unusual in fibroelastosis. In some instances conduction defects or paroxysmal tachycardia have been noted.

Cardiac catheterization has been performed in a few patients with proven endocardial fibroelastosis.[14] The right ventricle and pulmonary artery pressures have been normal or slightly elevated with elevation of the pulmonary capillary pressure. The features of constrictive pericarditis have been reported in adults with severe endocardial fibrosis.[15] This has not been a finding in fibroelastosis in infancy. Angiocardiograms reveal poor emptying of the left ventricle.[16, 17] This finding might support either the theory that the heart fails in endocardial fibroelastosis because the thick endocardial coating prevents proper cardiac contraction or that of primary muscle dysfunction.

Primary endocardial fibroelastosis is essentially a disease of infancy. Some cases survive into childhood, and an eleven-year-old child has been reported by Blumberg[18] and by Thomas.[6] A pathological counterpart of endocardial fibroelastosis similar to the primary syndrome of infancy has been noted in adults and reported under various titles.[19] However, it is not clear whether these cases indicate survival following the infantile syndrome or represent a separate entity. The course of the disease in infants may be somewhat variable. Eighty percent of the patients die by the age of one year.[20] We have observed two patients who succumbed during the neonatal period. Some infants die suddenly. Others improve temporarily with digitalis, oxygen and supportive therapy only to relapse on one or several occasions. In rare instances the improvement may continue and the patient reach childhood at which age the diagnosis of endocardial fibroelastosis can only be suspected. One is not justified in excluding this diagnosis in a given case merely on the basis of survival.

At post mortem examination one notes thickening of the mural endocardium involving both the fibrous and elastic tissues. The endocardium of the left ventricle is most frequently involved, that of the left atrium less so. Occasionally the process extends to the right side of the heart, involving both left and right, and in a rare case the endocardium of the right heart alone has been thickened.[7] The process may extend to involve the valves which then become thickened and deformed.[21] When valvular involvement exists, the mitral and aortic leaflets are most commonly affected. However, almost all valvular combinations have been described. There is considerable thickening of the myocardium which, in about 80% of the reported cases, is limited to the left ventricle.[21] The myocardial changes include degenerative processes, fibrosis and calcific deposits. The

alterations are most prominent in the sub-endocardial area and in the papillary muscles. Occasionally there may be perivascular hyperelastosis and fibrosis of the coronary arteries and also of the arteries in other organs.[5]

II. *Primary Myocardial Disease*

a. Idiopathic Myocarditis: This is a relatively uncommon disease in infancy characterized by an acute inflammatory involvement of the myocardium without any recognizable associated disease. It resembles the myocarditis seen as a complication of the acute infectious diseases. Pathologically there is hypertrophy and dilatation which is generalized or at times confined to the left ventricle. In one of our cases the degree of myocardial involvement was so extensive as to result in the formation of a ventricular aneurysm. Endocardial thickening may be a secondary phenomenon. Microscopic examination reveals evidence of acute inflammation as well as fibrosis and scarring. Aschoff bodies are not demonstrable and the valves are spared. The coronary arteries are normal.

Idiopathic myocarditis is probably caused by a variety of agents including bacteria and viruses. At times its distribution has been epidemic in character. The possibility of a viral etiology has recently been emphasized. Stoeber[22] reported 140 instances of this disease in infancy in which diffuse myocarditis was noted with little or no endocardial or pericardial involvement. A viral etiology was suggested but not proved. Amongst these cases the highest incidence was at approximately one year of age. Montgomery[23] reported on a group of newborns with acute myocarditis with isolation of Coxsackie group B virus from the feces of one fatal case and of one survivor. Javett et al.[24] reported an outbreak amongst newborns in South Africa in 1952. Ten infants were diagnosed as having acute myocarditis of whom six died. Coxsackie group B type 3 virus was isolated from the feces of one of the survivors. In a subsequent similar case they were able to recover this virus from the myocardium. A Coxsackie virus has also been isolated from the myocardium by Van Creveld[25] and by Kibrick and Benirschke[26] working in Enders' laboratory. The latter investigators isolated Coxsackie group B type 3 virus from the spinal cord of an infant dying from myocarditis on the seventh day of life and type 4 from the myocardium of a 10 day old infant. They postulate, as did Lind,[27] that the disease might be acquired in utero by way of transplacental transmission from a mother with a minor respiratory illness. Enders indicates that the Coxsackie B virus is the cause of some cases of acute aseptic myocarditis in infancy in addition to those cases of meningitis or encephalomyelitis in which there is associated myocardial involvement.

The clinical picture is similar to that caused by other conditions resulting in left ventricular hypertrophy in infants. The onset is sudden and the entire course may be a rapidly fatal one. Some are noted to have a relatively short biphasic pattern while, in others, a more chronic course measured in months has been noted. The disease varies markedly in severity and duration. Reports indicate that in the nonfatal cases recovery is complete without valvular or myocardial residua. Fluoroscopy and radiologic examination reveal general cardiac enlargement. The electrocardiogram demonstrates ST segment and T wave changes consistent with

myocardial anoxia or damage. In some, conduction defects are noted. The pattern of massive myocardial infarction has been simulated in one of our cases. The type and severity of the electrocardiographic changes are dependent upon the site and degree of myocardial involvement. Miller[29] believes that "a dependable electrocardiographic pattern of myocarditis" exists. It would seem that more data are necessary to substantiate this opinion. In our experience the electrocardiographic findings usually are of a non-specific nature similar to those seen in other conditions in the left ventricular hypertrophy syndrome.

b. *Glycogen Storage Disease of the Heart* is an exceedingly rare disorder resulting in the deposition of large amounts of glycogen in the myocardium and in striated muscle. This is commonly a familial disorder. The patients are normal at birth but acquire symptoms during early infancy. They gain and develop poorly. Tachycardia and dyspnea are early signs and tremendous cardiac enlargement is an early finding. Murmurs are conspicuous by their absence. Di Sant'Agnese et al.[30] noted macroglossia in several cases. Laboratory tests directed at evaluating glucose tolerance and glucose mobilization are normal. Ketonuria is not a feature of this disease. Roentgen findings are those of non-specific generalized cardiac enlargement. The electrocardiographic changes include T wave abnormalities similar to those found in other diseases of the left ventricular hypertrophy syndrome. In some, electrocardiographic evidence of left ventricular hypertrophy has been noted, but too few precordial lead studies are available to indicate the frequency of this observation. Death may occur suddenly or after an episode of congestive failure, usually before the end of the first year of life.

This disease is distinctly different from the type of glycogen storage disease in which the liver is predominantly involved. There is no gross involvement of the liver, but microscopic and chemical analysis reveal abnormal glycogen deposits in a large number of organs of the body. Abnormal amounts of glycogen are deposited in the myocardium and in striated muscle. The heart has a distinctive post mortem appearance as noted by Andersen. It is enormously enlarged, round in shape, with a homogeneous appearance of the myocardium. Microscopically the myocardial fibers are very large and vacuolated. The pathogenesis of this metabolic disease is poorly understood.

A family history indicating that other infants had died under similar circumstances as well as the finding of cardiomegaly and macroglossia should suggest cardiac glycogen storage disease as a diagnostic possibility. Skeletal muscle biopsy should be performed and may reveal excess glycogen storage. At the present time the prognosis is universally bad. There is no satisfactory treatment for this disease.

c. *Tumors:* Primary tumors of the heart are rare in infancy. The most common type is the rhabdomyoma. Kidder[31] found a total of 69 such tumors in his review of the literature; half were discovered in the first year of life. They are often found in patients with tuberous sclerosis. The heart is enlarged and the characteristics of the left ventricular hypertrophy syndrome may be noted. Murmurs may or may not be present depending upon whether the tumors are in or upon a valve with resultant

obstruction of blood flow. Arrhythmias have been noted frequently. As a rule, death occurs as a sudden event.

Fibroma of the myocardium, myxoma of the atrium and rhabdomyosarcoma have also been observed in infancy. A recent report[32] describes a rhabdomyosarcoma in an infant four months of age in whom the myocardium and left coronary artery were involved. Electrocardiographic signs of non-progressive, marked ST segment elevation in the precordial leads V_2-6 was present in this infant with cardiac failure resistant to medical therapy.

d. *Nutritional Deficiencies:* It is well known that diets deficient in vitamins may produce myocardial damage in experimental animals and in humans. The human heart is affected in thiamin deficiency and possibly in scurvy. In beriberi heart disease the underlying physiologic change is peripheral arteriolar dilatation acting much like a large arteriovenous fistula associated with fatty degeneration of the myocardium. Vitamin B deficiency in infancy is not a common cause of cardiac hypertrophy in the U.S.A. although its exact frequency is difficult to ascertain. The possibility of a nutritional and vitamin deficiency should be considered in allergic infants receiving elimination diets. A fatal instance of an infant on such a diet developing beriberi associated with encephalopathy was observed by Davis and Wolf.[33] A therapeutic trial of thiamin should result in a decrease in the size of the heart and reversion of flat or inverted T waves although this reversibility has not been noted in some advanced cases.

III. *Inadequate Coronary Blood Flow*

a. *Anomalous Origin of the Left Coronary Artery:* Several types of variation in anomalous origin of the coronary arteries have been described. A single coronary artery may arise from the aorta to supply the entire myocardium. This usually does not cause any ill effects. Anomalous origin of both coronary arteries from the pulmonary trunk is an exceedingly rare anomaly resulting in early death.[34] Origin of the right coronary artery from the pulmonary artery with normal origin of the left coronary artery has been described in asymptomatic patients.[35] Origin of the left coronary artery from the pulmonary artery is a rare anomaly that has been frequently described.

The clinical picture of anomalous origin of the left coronary artery resembles very closely that seen in other examples of the Left Ventricular Hypertrophy Syndrome. Feeding difficulties commence in early infancy and are followed by the development of cardiac failure. The literature contains frequent reference to angina-like attacks which are said to be peculiar to, and typical of, an anomalous left coronary artery. These attacks are precipitated by feedings or by other exertional efforts. We believe these attacks are noted in infants with myocardial ischemia from a variety of causes and are not diagnostic of this anomaly. They are not present in all patients with this anomaly and they have been observed in patients with other lesions causing the left ventricular hypertrophy syndrome. We have observed these symptoms in an infant with endocardial fibroelastosis. House[36] reported a one-year-old child with idiopathic myo-

carditis who had anginal attacks with pain, sweating and pallor. Similar attacks have been reported by Engel[32] in an infant with rhabdomyosarcoma. It is apparent that a history of attacks simulating angina have no specific diagnostic importance. They are of importance in suggesting the possibility of the left ventricular hypertrophy syndrome.

Upon examination, the heart is found to be markedly enlarged with primary involvement of the left ventricle. Significant murmurs are not heard. Radiologic examination reveals the presence of a large globular shaped heart. Occasionally left ventricular enlargement or aneurysmal dilatation is noted. Electrocardiographic studies of some of the first reported cases revealed inverted T waves in standard leads I and II with low voltage and ST segment deviations. These abnormalities were believed to be pathognomonic of the presence of an anomalous left coronary artery. It is now recognized that these changes are the result of myocardial anoxia and may be produced by a variety of lesions. Precordial leads often reveal deep Q waves and marked ST segment deviation suggestive of myocardial necrosis. Such changes are seen most often in lesions producing inadequate coronary blood flow and may be helpful in diagnosis. However if damage to the myocardium is sufficiently extensive from other causes, one can expect such electrocardiographic aberrations. Furthermore, abnormal electrocardiograms are not found in all cases of anomalous origin of the left coronary artery. A similar occurrence was reported by Tedeschi and Helpern.[34] The time when the electrocardiogram is taken in relationship to the pathogenesis of this anomaly is important. In a recent experience, the first electrocardiogram demonstrated minor T waves changes. Subsequently a myocardial infarction occurred resulting in diagnostic electrocardiographic changes indicative of severe myocardial necrosis. This was confirmed by post-mortem examination. Aortography may be a useful adjunct in establishing the presence of an anomalous left coronary artery. Injection of dye into the aorta may permit radiographic visualization of the coronary arteries and their origin.[37]

The clinical course is characteristically that of rapid progression following the onset of symptoms. In most cases death occurs in the first year of life.[38] There are reports, however, of persons with this condition who reached adulthood and then succumbed suddenly or after progressive angina and heart failure.[39-41]

At post-mortem examination the anomalous origin of the left coronary artery is noted. The more common form is the origin of the anterior descending branch from the pulmonary artery or conus while the circumflex arises from the aorta. However the entire left coronary artery may have an anomalous origin. Bland, White and Garland[41] demonstrated that scarring of the myocardium occurs, being concentrated usually toward the endocardial side of the anterior wall of the left ventricle and septum following the distribution of the left coronary artery. There may be severe myocardial necrosis, aneurysmal dilatation of the apex of the left ventricle and, on rare occasions, rupture of the myocardium with resultant hemopericardium.[42, 43] Endocardial fibroelastosis involving the dilated left ventricle is a very common secondary manifestation of this anomaly.

It is of practical importance to establish, ante mortem, the existence of the abnormal origin of the left coronary artery. Surgical correction,

aimed at increasing the oxygen content of blood entering the anomalous coronary artery, has been attempted.[14] Edwards[44] suggests that the relative oxygen unsaturation of blood in the coronary artery is not the cause of myocardial necrosis. Low pulmonary artery blood pressure may be inadequate for maintenance of adequate coronary circulation to the left ventricle. One can anticipate continuing efforts directed towards surgical correction.

b. *Coronary Occlusive Disease:* The adult form of atherosclerosis or arteriosclerosis has not to our knowledge been described as a cause of heart disease in infancy but other forms of coronary artery disease do occur although they are very rare. Stryker[45] has classified and discussed this group of lesions.

Medical sclerosis of the coronary arteries is the most common form of occlusive disease in infancy.[46] Sclerosis and calcification are found in the media and fibrous proliferation of the intima occludes the lumina of the vessels. Myocardial infarcts have resulted.[47] No lipoid deposits occur. Thrombi may be present within the lumina. Thomas[48] reports the association of endocardial fibroelastosis with arterial calcification and myocardial infarction. In almost all cases there is generalized arterial involvement, many organ systems being affected. Coronary occlusive disease in infancy may be "idiopathic" and result in death in very early infancy. A genetic defect in the arterial elastic tissue has been suggested.[49] Some cases are secondary to renal hyperparathyroidism due to severe anomalies of the kidneys.[50]

The clinical picture is that noted in other lesions in this syndrome. Lipman[51] has suggested that the ocular fundi may show evidence of arteriolar damage. Andersen and Schlesinger[50] reported calcification of arteries in the upper extremities seen on x-ray films obtained for possible changes in the radius and ulna, while Cochrane[52] suggests the possibility of demonstrating calcified vessels in the neck in this manner. The electrocardiogram may reveal evidence of nonspecific myocardial anoxia, left ventricular hypertrophy or of myocardial infarction.

DISCUSSION

In order to establish the presence of the left ventricular hypertrophy syndrome, it is important to demonstrate anatomic left ventricular hypertrophy in an acyanotic infant with absent or insignificant cardiac murmurs. This is not an easy task in early infancy. Displacement of the apex impulse downwards and to the left and the presence of a heaving apical thrust usually are present if significant left ventricular hypertrophy exists. A parasternal lift is usually associated with right ventricular hypertrophy. However, this is not always obvious. The generally accepted radiographic criteria of chamber enlargement are not necessarily valid in infancy. Often left ventricular hypertrophy produces a heart of rather globular shape with deviation of the esophagus posteriorly and to the right. The angiocardiogram offers the most objective evidence of cardiac enlargement and is of diagnotic value, but we do not suggest that this procedure is necessary or advisable in all circumstances.

The electrocardiogram may demonstrate evidence of myocardial anoxia or damage. Abnormalities include ST segment depressions or elevations, and T wave depressions or inversions in one or more standard and unipolar leads. Low voltage may be present. These changes are not specific for any particular anomaly but are characteristic of any disease or malformation which results in myocardial anoxia or damage. Similar electrocardiographic changes are associated with digitalis effect upon the myocardium. The myocardium may be affected by a variety of noxious agents and yet will react electrocardiographically in a uniform fashion. We do not believe the electrocardiogram has pathognomonic features. The demonstration of electrocardiographic findings in infancy simulating those of an acute myocardial infarction suggests severe disturbance of coronary circulation. These have been observed in idiopathic myocarditis,

tumors of the heart, coronary occlusive disease as well as in anomalies of the coronary arteries.

The electrocardiogram is often of value in the identification of specific chamber enlargement. Precordial tracings may reveal the presence of unequivocal left ventricular hypertrophy. Electrocardiographic criteria are available for the diagnosis of left ventricular hypertrophy.[53] These criteria are based on the normal limits of various deflections in each age group. The finding in an infant of the typical adult R/S ratio progression from right to left-sided chest leads is strongly suggestive of the presence of left ventricular hypertrophy. The absence of the criteria necessary to establish the presence of left ventricular hypertrophy in an infant's electrocardiogram, however, does not eliminate the existence of such hypertrophy. The electrocardiogram represents the balance of forces between the two ventricles. Beyond early infancy, the normal balance of electrical forces during ventricular depolarization depends upon a left ventricle which is anatomically dominant over the right; therefore an electrocardiogram which indicates a normal balance by adult standards actually reflects some left ventricular preponderance. In order for the classical pattern of left ventricular hypertrophy to appear in the electrocardiogram, considerable hypertrophy must exist. Consequently a "normal" electrocardiogram in an infant does not exclude the presence of lesser degrees of left ventricular hypertrophy.

We must next consider the electrocardiographic diagnosis of right ventricular hypertrophy for, if one could demonstrate unequivocally the presence of anatomic right ventricular hypertrophy in a given infant, this would exclude the existence of the left ventricular hypertrophy syndrome, except in neonates. In young infants, normal physiological and anatomical right ventricular preponderance exists; pathological left ventricular hypertrophy could thus be present and yet be masked for a time. As normal maturation proceeds, there is less and less anatomic right ventricular preponderance until, finally, the left ventricle predominates.

This normal development from right to left ventricular preponderance in early infancy is reflected in both the electrocardiogram and the vectorcardiogram.[54, 55] We have found the latter particularly helpful in this regard. In the normal neonatal state of anatomic right ventricular predominance, the vectorcardiographic pattern is that associated, in older children and adults, with pathological right ventricular hypertrophy. (In the transverse plane, there is clockwise rotation of the QRS loop and displacement of the loop to the right and anteriorly). The electrocardiogram, as can be predicted from the vectorcardiographic pattern, reveals tall R and small s waves in right-sided chest leads. After a period of several weeks or months, the vectorcardiogram displays a normal counterclockwise rotation of the QRS loop in the transverse plane. However, the loop is still displaced anteriorly and to the right. This displacement causes, in the electrocardiogram of infants of this age, persistence of the neonatal tall R and small s waves. At this time it may be difficult to differentiate the electrocardiogram of this "normal infant pattern" from that produced by persistent and pathological right ventricular hypertrophy. However, we believe that the vectorcardiographic configurations are so characteristically dissimilar after the neonatal period that one can easily distinguish the "normal infant pattern" from that of pathological right ventricular hypertrophy.

Electrocardiographic criteria of left ventricular hypertrophy are difficult to establish in infancy. The absence of the criteria for right ventricular hypertrophy in an infant with an enlarged heart is therefore of considerable importance. Under these circumstances we believe the vectorcardiogram is more accurate than the electrocardiogram in the first year of life.

In our experience and that of others, the axis deviation as determined from the standard leads of the electrocardiogram is of less diagnostic value. Left axis deviation occurs not infrequently in patients with right ventricular hypertrophy and vice versa.

SUMMARY

In infants a group of cardiac lesions exist which produce cardiac enlargement, predominantly of the left ventricle, without the presence of significant murmurs or central cyanosis, and in which there is a tendency to the development of heart failure. Under these circumstances the electrocardiogram may be normal, reveal evidence of myocardial anoxia or of left ventricular hypertrophy. We have called this complex the *Left Ventricular Hypertrophy Syndrome*.

This syndrome does not include more commonly occurring cardiac anomalies which produce left ventricular hypertrophy associated with significant murmurs. It does include (1) primary endocardial fibroelastosis, (2) predominantly myocardial disorders such as (a) idiopathic or aseptic myocarditis, (b) glycogen storage disease of the heart, (c) tumors of the heart and (d) nutritional deficiency states causing myocardial dysfunction; and (3) disorders resulting predominantly in abnormalities of coronary blood flow as (a) anomalous origin of the left coronary artery and (b) coronary occlusive disease.

The demonstration of left ventricular hypertrophy in infancy by physical examination, x-ray film and electrocardiography is discussed and the usefulness of vectorcardiography in delineating pathological right ventricular hypertrophy and thereby ex-

cluding a diagnosis of left ventricular hypertrophy syndrome is emphasized.

The prognosis for survival beyond infancy is grave in these patients and the differentiation from congenital cardiac malformations is important.

RESUMEN

Existe un grupo de lesiones cardiacas en los infantes que producen crecimiento del corazón con predominio en le ventrículo izquierdo sin que haya murmullos de significación ni cianosis central y en los que hay tendencia al desarrollo de insuficiencia cardiaca.

En esas circunstancias el electrocardiograma puede ser normal o bien revelar anoxia cardiaca o hipertrofia del ventrículo izquierdo. Hemos llamado a este complejo el Síndrome de hipertrofia Ventricular Izquierda.

Este síndrome no incluye las anomalías más corrientes del corazón que producen hipertrofia ventricular acompañda de murmullos evidentes. Incluye los siguientes: 1) Fibroelastosis endocárdica primaria, 2) trastornos predominantes del miocardio tales como a) miocarditis aséptica o idiopática, enfermedad por acumulación de glucogeno en el corazón, c) tumores del corazón, d) estados de deficiencia nutricional causantes de disfunción miocárdica; y 3) trastornos resultantes de predominio de anormalidades del flujo coronario tales como: a) origen anómalo de la arteria coronaria, y b) enfermedad coronaria oclusiva. La demostración de hipertrofia ventricular izquierda en la infancia por el examen físico, los rayos X y la electrocardiografía se discuten y se recalca la utilidad de la vectocardiografía la delinear la hipertrofia ventricular derecha y de ese modo se excluye el diagnóstico del síndrome de hipertrofia ventricular izquierda.

El pronóstico para la sobrevida más allá de la primera infancia es grave en estos enfermos y es importante la diferenciación de las malformaciones congénitas.

RESUME

Chez les petits enfants, il existe une catégorie de lésions cardiaques qui provoquent une hypertrophie cardiaque, atteignant principalement le ventricule gauche, sans qu'il y ait de souffles notables ni de cyanose. Cet état a tendance à évoluer vers l'insuffisance cardiaque. Dans ces conditions l'électrocardiogramme peut être normal, ou apporter la preuve d'une anoxie myocardique ou d'une hypertrophie du ventricule gauche. Nous avons appelé ce complexe le "syndrome d'hypertrophie ventriculaire gauche".

Ce syndrome ne comprend pas les anomalies cardiaques beaucoup plus banales qui entrainent une hypertrophie ventriculaire gauche, mais comportent des souffles importants. Il comprend: 1°) la fibro-élastose endocardique primaire; 2°) les troubles myocardiques prédominants, tels que: a) la myocardite aseptique ou idiopathique, b) l'affection cardiaque à surcharge glycogénique, c) les tumeurs cardiques, d) les états de déficience nutritionnelle provoquant une dysfonction myocardique; 3°) les troubles résultant de façon prédominante des anomalies du débit coronarien tels que: a) origine anormale de l'artère coronaire gauche, et b) affection occlusive coronarienne.

La mise en évidence de l'hypertrophie ventriculaire gauche dans l'enfance par l'examen physique, la radiologie et l'électrocardiographie est discutée, et l'auteur insiste sur l'utilité de la vectocardiographie pour préciser l'existence de'une hypertrophie ventriculaire droite et exclure ainsi un diagnostic de syndrome d'hypertrophie ventriculaire gauche.

ZUSAMMENFASSUNG

Bei Kleinkindern findet sich eine Gruppe mit Herzveränderungen, gekennzeichnet durch Herzvergrösserung, vorwiegend am linken Ventrikel, ohne Vorliegen nennenswerter Geräusche oder zentraler Zyanose, und bei denen eine Tendenz zum Zustandekommen eines cardialen Versagens besteht. Unter Umständen kann das Elektrokardiogramm normal sein, das Bestehen myocardialer Anoxieanzeichen oder eine Hypertrophiedes linken Ventrikels. Wir haben diesen Krankheitskomplex bezeichnet als *"Linksseitiges Kammerhypertrophie-Syndrom."*

Dieses Syndrom enthält keine der häufiger vorkommenden cardialen Anomalien, die mit einer linksseitigen Kammerhypertrophie verknüpft sind mit nennenswerten Geräuschen. Eingeschlossen sind (1) primäre endocardiale Fibroelastose (2) überwiegend myocardiale Störungen wie (a) idiopathische oder aseptische Myocarditis, (b) Glykogen-Speicherkrankheit des Herzens, (c) Tumoren des Herzens und (d) agimantäre Mangelszustände mit nachfolgender myocardialer Dysfunktion; (3) Störungen als Folgen besonders bei Veränderungen der koronaren Zirkulation wie (a) Anomalien Im Ursprung der linken Coronararterie und (b) zu Coronarverschluss führende Krankheit.

Der Nachweis der linksseitigen Kammerhypertrophie während der frühesten Kindheit durch physikalische Untersuchung, Röntgenaufnahme und Elektrokardiographie wird besprochen und der Wert der Vektorkardiographie zur Abgrenzung pathologischer rechtzeitiger Kammerhypertrophie mit daraus sich ergebendem Ausschluss eines linksseitigen Kammerhypertrophie Syndromes hervorgehoben.

Die Prognose hinsichtlich des Überlebens der ersten Kindheit ist ernst bei solchen Kranken und die Abgrenzung gegenüber kongenitalen cardialen Missbildungen ist bedeutsam.

References will appear in reprints.

The Surgical Treatment of Coronary Heart Disease: a Review and Critique of the Literature*

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In the United States, heart disease is the leading cause of death, outranking malignancies, accidents, pneumonia, and tuberculosis. One of every two persons will die of some form of heart disease. This increase in incidence, making it the number one killer in the nation, is both relative and absolute: as the infectious diseases are being brought more and more under control, and the standard of living and the life expectancy of the average American are steadily climbing, the insidious and chronic diseases become more prominent. Statistics, however, clearly show that there has been an absolute rise in the incidence of heart disease over the past 20 years or so. The direct cause of this rise is the greatly increased incidence of coronary heart disease. Since 1930, with the exclusion of coronary disease, heart disease has steadily decreased, whereas coronary disease *per se* has rapidly increased.

As our understanding and hence, symptomatic treatment of coronary heart disease have improved, the relative prognosis of people suffering from this condition has improved. In 25 year follow-up studies of 200 patients with myocardial infarctions, and 456 with angina pectoris, Richards, Bland and White[1] have reported the following: the average survival of patients from the onset of angina pectoris symptoms is about 10 years; 76 per cent of these patients die of cardiac causes. Angina pectoris does decrease the average life expectancy, but not exceptionally so; in other words, at any given age, 7 per cent of men and 5.3 per cent of women with angina pectoris, in addition to the predicted mortality of the population at large, will die. Turning to myocardial infarction, the average survival time is five years, considering the total number of patients. Those who completely recover from the initial attack, however, have an average survival rate of better than 10 years.

Medical and Surgical Approaches Compared

The statistics quoted above concerning prognosis point out that coronary heart disease is not universally fatal over a short span of time, and that modern medicine can successfully combat the nation's leading cause of death. It cannot be questioned that prompt medical therapy (morphine, rest, oxygen, anticoagulation, etc.) is greatly responsible for the encouraging trend in prognosis; but regardless of present advances and advances to come, strict medical therapy for the coronary heart disease patient is purely a symptomatic and "hold the fort" approach. There are two opportunities open today for a more definitive approach to the problem: 1) the prophylactic prevention of coronary atherosclerosis by diet or other means, and 2) the correction of the circulatory problem once it has come into existence.

*This paper was compiled from an essay written by the author during his senior year at the College of Physicians and Surgeons, Columbia University, and was selected as the second prize winning essay in the American College of Chest Physicians 1957 contest.

The latter approach, the surgical treatment of coronary heart disease, is the topic of this paper. Before entering into the work done in the field today, it would be advantageous to outline the eventual objectives of surgical therapy:

1. Increase the life expectancy of patients with coronary heart disease.
2. Decrease pain; i.e., angina pectoris.
3. Decrease work limitations; return patients to relatively active existence
4. Prevent myocardial infarctions.
5. If not prevent myocardial infarction, convert what would have been a fatal infarct to a non-fatal one, and convert what would have been a large infarct to a smaller one.
6. Possibly prevent death by ventricular fibrillation. Autopsy series of patients dying of coronary occlusion reveal no tissue damage (cardiac wall necrosis) in one third of the cases, and in only 10 per cent of the hearts is damage so severe that one can say it is incompatible with life; likewise, patients die of coronary occlusion with a small area of infarction, and other patients having died of an unrelated cause have massive old infarcts. On the basis of this evidence, Dr. Claude Beck[2] postulates that the 90 per cent with no, or only a small amount of, visible damage, die as result of ventricular fibrillation, brought on by what he calls an electrically unstable heart. In dogs, he has shown with direct cardiac wall electrocardiography, that there is a potential difference between a normal area of myocardium and an ischemic one, caused by coronary narrowing, and that at a critical potential difference, this heart can be sent into ventricular fibrillation.

Surgical Techniques Utilized

There are two leading schools of approach to the problem today: there are those, primarily Thompson and Beck, who advocate revascularization through the development of new anastomotic channels, and Vineberg's group, who advocate implantation of an already functioning artery into the heart muscle directly.

Beck Procedure[3] (the one he now finds most successful in leading to the development of intercoronary anastomic channels).

1. Parietal pericardium and surface of heart are abraided by burrs—to provide raw surfaces for granulation tissue ridges.
2. Two tenths of a gram of coarsely ground asbestos is applied to the heart surface—to stimulate formation of granulation tissue and new arterial channels.
3. The coronary sinus is occluded to a diameter of 3 mm.—to provide back pressure and thereby, greater filling of small collateral radicals.
4. Parietal pericardium and mediastinal fat are applied to the surface of the heart—to provide a source of ingrowing vascular granulation tissue.

Thompson Procedure.[4] Thompson only inserts a non-absorbable and irritating substance into the pericardial sac; he uses magnesium silicate (talc).

Vineberg Procedure.[5] Implantation of the left internal mammary artery into the left ventricle via a myocardial tunnel—on the basis that atherosclerosis occurs in the epicardial part of the coronaries and not the myocardial part which is rich in patent communications; therefore, this procedure is essentially a by-pass operation of an obstructed circulation.

Animal Experimentation

Before any of these procedures were attempted on man, a large amount of animal experimentation was carried out. Outlined below is some of the more interesting work designed to show the efficacy of these methods.

Beck.[2] By utilizing the Mautz-Gregg backflow technique, which essentially consists of measuring the backflow blood from the distal end of a cut coronary artery, the proximal end having been ligated, Beck showed that his procedure adds 4.7 c.c. of blood per minute, or 282 c.c. per hour, to an area of myocardium made ischemic by complete ligation of the artery that normally supplies this area. This increase in backflow has been found intact one year after operation. He has also shown that this increase in backflow has decreased the mortality in dogs whose coronaries were ligated after the Beck procedure had been performed, and that the size of the percipitated infarction, if any, was measurably reduced.

Vineberg.[5] Vineberg has set up five rigid dog laboratory criteria for a successful revascularization operation, and he has data to show that his procedure fulfills all of his conditions. His criteria are:

1. The anatomic demonstration of functioning vessels of arteriolar size (over 40 microns in diameter) by injection methods (Schlesinger injection lead acetate-agar-mass), serial sections, etc., present between the coronary circulation and the extracardiac source of blood over a period of six months and longer.
2. Survival without infarction post ligation of one of the major coronary vessals. Eighty per cent of controls (no Vineberg procedure) died post ligation, and the other 20 per cent survived with infarction. All of the dogs receiving the Vineberg operation survived the coronary ligation without infarction.
3. Subsequent interruption of the extra-coronary circulation should lead to immediate death or survival with a large infarct; this occurred in Vineberg's own series.
4. Increased flow to heart muscle fibers by oxygen consumption studies. The heart is arrested and perfused via the internal mammary artery implant, and as the oxygen saturation drops from 98 per cent at the internal mammary artery, to 40 per cent at the coronary sinus, the heart starts to beat again, demonstrating not only that blood travels through the heart from the internal mammary artery implant, but that blood is brought into close approximation with the myocardial fibers, allowing them to make use of the blood oxygen content.
5. The satisfactory treatment of artificially produced coronary artery insufficiency: cellophane is wrapped around the anterior descending branch of the left coronary artery during the first operative procedure, providing a focus for surrounding fibrosis, and thereby simulating the gradual coronary occlusion of atherosclerosis. In

three months the animals showed a marked reduction in exercise tolerance on a treadmill. Then one half of the dogs receive the revascularization procedure; further evaluation tests are carried out on the treadmill in another three to five months, when the animals that had received the Vineberg implantation operation had regained a substantial amount of exercise tolerance, coming close to their average pre-experiment treadmill time; whereas the animals who did not have the Vineberg operation at the three month mark had, at the end of six to eight months post-cellophane occlusion, very severe exercise tolerance reduction. (Table I)

Sewell.[6] Some interesting work, as yet unpublished, has been done by Dr. William Sewell at the Albany Hospital, who, by a technique similar to Vineberg's has evidence that the development of a collateral anastomotic bed between the extra-cardiac source and the coronaries is a function of need; i.e., an area of ischemia and hence, relative hypotension to the extra-cardiac source stimulates the formation of anastomotic channels, whereas, without the presence of ischemia and a relatively low pressure area, the stimulus for the development of collateral channels is far less. Vineberg himself has some data to show that in non-ischemic hearts the average anastomotic rate is 46 per cent with 67 per cent open vessels, whereas, in ischemic hearts, the average anastomotic rate is 71 per cent with 86 per cent open vessels.

Selection of Patients for Surgery

Turning to the evaluation of these procedures in human subjects, the first consideration is the selection of patients.

Indications (based primarily on Beck's[7] indications).

1. Patients with a strong family history of coronary heart disease; the only case done to date for this reason by Beck was a patient whose father, uncle, and two brothers died of coronary heart disease.
2. Severe angina pectoris.
3. Patients with one or more myocardial infarctions, with normal or slightly increased heart size, and able to work; the majority of patients fall within this classification.
4. Patients with previous infarctions, greatly increased heart size, unable to work; if one aids these patients, it is to be considered strict salvage; they represent the majority of mortality figures.

Contraindications.

1. Active failure and greatly enlarged heart size.

TABLE I—VINEBERG, ET AL.: FOUR YEARS CLINICAL EXPERIENCE WITH INTERNAL MAMMARY ARTERY IMPLANTATION*

(Treadmill Time: 8½ mph)	Tolerance Time in Minutes
Average pre-experiment	9-12
3 months post coronary occlusion (all dogs)	2.5-4
No implantation: 6-8 months post coronary occlusion	1.6
3 months post implantation operation, and 6 months post coronary occlusion	6-8

2. Less than six months post infarction.
3. Progressive disease; infarct following infarct.
4. Suddenly increasing angina pectoris; this may be a sign of an impending myocardial infarction, and is an indication to delay surgery.

Results of Coronary Heart Disease Surgery

The following are the statistics dealing with the results of coronary heart disease surgery, compiled by the men who have done the major part of it:

Beck.[8] In a series of 192 patients, Beck reports improvement with respect to pain (i.e., angina pectoris) in 84.8 per cent, with 36.3 per cent having no pain, and 48.5 per cent only mild pain after the procedure; whereas previous to the operation, the group reported on all had moderate to severe angina pectoris. He reports improvement with respect to work limitation in 78.6 per cent, 27.2 per cent having no, and 51.4 per cent having some residual limitation after surgery. His overall operative mortality is 6.6 per cent, over the last 100 operations, however, his mortality was 0 per cent. Beck compares his one year and two year follow-up results with a series of 88 patients of Lindgren's,[9] admitted to the hospital for, but one reason or another, not receiving sympathectomy for severe angina pectoris. Beck's one year mortality (not including operative mortality) was 6.6 per cent, Lindgren's was 17 per cent, and at the two year mark, Beck's mortality figure was 18 per cent, and Lindgren's was 30 per cent.

Thompson.[4] In a series of 57 patients, Thompson reports 90 per cent of patients improved more than 50 per cent, and 40 per cent improved more than 75 per cent, with respect to the pain of angina pectoris and work limitation. His operative mortality is 12 per cent. His 14 years' experience with his operation reveals an average post-operative survival time of nine and a half years. He has some post mortem 10 year follow-up specimens which reveal that the adhesive granular pericarditis is continuous (i.e., foreign body particles are not absorbed), that no permanent (non-granulous) scar is formed, that the anastomotic channels are permanent and patent, and that constrictive pericarditis does not occur.

Vineberg.[5] Finally, in a small series of 29 patients, Vineberg reports 70 per cent improvement with respect to the categories of pain and work limitations, and an operative mortality of 4.3 per cent (Cumulative Table II).

DISCUSSION

There has been a good deal of criticism, in and out of the literature, leveled at the surgical treatment of coronary heart disease. One of the earliest arguments advanced against the experimental approach in dogs was that the coronary circulation pattern varies considerably from animal to animal; it is argued, therefore, that individualistic canine patterns might influence accumulated data, and that *scientific* repetition of an experiment by different investigators would be impossible. This objection can probably be overcome by using a large enough series of animals (Beck has now done over 5000 operations on dogs), and by specifying and standardizing the exact sites of undertaken manipulations. Within a large series individual idiosyncrases would become negligible if the overall results were found to be statistically significant.

A more damaging criticism of animal experiments is leveled by Blumgart and Paul,[10] who question extrapolation from experimentation done on the hearts of normal dogs to clinical operations on ischemic human hearts. In the quoted article, these authors offer three illustrations from the literature to substantiate their point of view: Work done by Schlesinger and Blumgart using the Schlesinger lead acetate-agar injection mass, which will only fill vascular channels over 40 microns (80 microns in fresh

TABLE II
CUMULATIVE RESULTS OF BECK,[10] THOMPSON,[7] AND VINEBERG[8]

	Beck (192 pts.)	Lindgren (88 pts.)	Thompson (57 pts.)	Vineberg (29 pts.)
Improvement of angina:			90 per cent improved over 50 per cent	70 per cent improved
no pain:	36.3			
mild pain:	48.5			
	84.8 per cent			
Work limitation improvement:			40 per cent improved over 75 per cent	
no limitations:	27.7			
some limitations:	51.9			
	78.6 per cent			
Operative mortality:	6.6 per cent (0 per cent of past 100 pts.)		12 per cent	4.3 per cent
1 year mortality:	6.6 per cent	17 per cent	average post operation survival is 9½ years	
2 year mortality:	18 per cent	30 per cent		

specimens) in diameter, demonstrated that intercoronary anastomosis of that size exist in only 15 per cent of normal hearts, but in the presence of coronary narrowing or occlusion, they are abundant and exist in close to 100 per cent of ischemic hearts. This network is so rich indeed that Blumgart and Paul find it difficult to conceive how it can be further increased by surgical means. Eckstein and Leighninger in 1954 showed that the long-term protection against coronary ligation in dogs receiving the Beck aorta to coronary sinus anastomotic procedure was the result of the stimulation of a functional intercoronary collateral bed, and not any direct aortic flow to the heart via the coronary sinus, since this communication sclerosed and closed down, six to eight weeks after the graft procedure. The conclusions drawn from this by Blumgart and Paul are that since grafting does not add a sustained flow of new arterial blood to the heart, and that since intercoronary anastomoses already exist in the ischemic human heart, it is not justifiable to do a procedure to establish a status which already exists. Finally, the authors refer to Burchell's article which pointed out that the epicardium was a barrier to supplying any substantial flow of blood to the myocardium from surgically produced pericardial adhesions.

What defense can cardiac surgery offer against these criticisms? Considering them in reverse order: attempts to remove Burchell's epicardial barrier are seen in the work of Harken and his group,[11] Beck and Vineberg. Harken removes the epicardium by painting it with 95 per cent phenol, and finds that three months after this procedure arterial communications exist via the pericardial adhesions, and that therefore, a successful deepicardialization is easily feasible and that subsequent extracoronary anastomotic communications can develop between the myocardium and the pericardial adhesions. Beck removes the epicardial barrier with his burring operation early in his procedure, and Vineberg bypasses the epicardium through the use of his myocardial tunnel.

Turning to the aortic to coronary sinus graft failure, Beck soon realized that his attempt at an arterial retrograde venous shunt had, as its only lasting results, the coronary anastomoses achieved by the handling of the tissues, for the venous drainage system of the heart does not seem to be able to handle arterial pressures over any length of time, He abandoned, therefore, this more complicated procedure, involving two operative manipulations (one to establish the graft, and in two to three weeks, re-entering to narrow down the coronary orifice), in favor of the Beck operation previously outlined. That no external arterial blood flow *per se* can be brought directly to the heart has been essentially disproved by the work of Vineberg, who has demonstrated patent communications, open over six months time, between the extracardiac source of blood (the internal mammary atery implant) and the coronaries, through the use of the Schlesinger injection mass. Furthermore, as has been shown by both Vineberg and Sewell, an ischemic heart, the heart Blumgart states cannot be benefited by surgery, stimulates the development of an even higher percentage of patent extra-coronary arterial communications.

As to the question of intercoronary anastomoses, and the question of whether one is justified at all in extrapolating from animal data to human surgery, only time and the accumulation of human data will tell. Can surgery benefit the heart already rich in intercoronary anastomoses? Only a critical evaluation of postoperative human statistics can answer that question. Likewise, justification for the transference of animal data to the human sphere is a function of, not only in experimental surgery, but in all animal research, the human results from that transference.

This leads directly to an analysis of the criteria used to judge data in this field today. Beck, Thompson, Vineberg, Harken, etc., all measure their results in terms of relief of pain (angina pectoris) and a return to a relatively active life. These criteria have been attacked by many, including Blumgart and Paul, on the grounds that these are subjective criteria, capable of being influenced by the patient's emotional expectations; and that operative manipulations might eliminate pain by the cutting of sensory fibers, and not by actually increasing the blood flow to cardiac muscle. Most cardiac surgeons would refute the idea that the techniques utilized today for coronary heart disease surgery could destroy the major sensory outflow of the heart. It cannot be denied that pain is a subjective finding, and that individuals vary in their suggestibility with respect to the severity of the pain. We are, however, willing to take the subjective word of the patient that the sublingual insertion of nitroglycerine or the subcutaneous injection of morphine relieves the pain of angina pectoris and myocardial infarction. And furthermore, the patient with true severe angina pectoris will not be cured of his disease or greatly relieved of it by suggestions and the aura of surgery alone.

The other criteria of evaluating human data are an increase in the life span of patients with coronary heart disease, and a decrease in the number and size of any ensuing infarcts. Blumgart and Paul call this almost impossible to evaluate due to the inherent unpredicability of the clinical course of the disease. This attitude is rather a defeatist one as well as being rather unimaginative with respect to the excellent existing statistics concerning coronary heart disease. The 25 year follow-up series of 200 patients with myocardial infarction, and 456 patients with angina pectoris, by Richards, Bland and White, give us an excellent picture of the prognosis of patients with coronary heart disease (receiving good medical care and follow-up)

originally diagnosed in the 1920s. Future series (e.g., long-term follow-up of patients who have been anti-coagulated) might even be more optimistic, and at any rate, will provide an average life expectancy figure for patients on medical therapy alone that surgical series of the future must overshoot if they are to prove that surgery prolongs life. Thompson, who has obtained an average life expectancy of nine and a half years in his series of 57 patients, compares quite favorably with the five or six (counting immediate death from infarction or not) year life expectancy of the myocardial infarct patient in Richards, Bland, and White's series. Thompson's patients cannot be compared against the 10 year survival of patients with complete recovery after the initial attack, for none of his patients were free of symptoms prior to surgery; on the contrary, his patients were the ones with the severest post infarction incapacitation.

One highly justified criticism leveled against the surgeons doing procedures for coronary heart disease is that they, outside of the national statistics, the Richards, Bland, and White series being an example, have no good control group. The Lindgren group with which Beck compares his statistics is not a comparable matched group of controls. It would seem an absolute necessity at this time that one of the leading surgical groups in the field, in conjunction with its hospital's medical staff, study, on a long-term follow-up basis, a large series of two well-matched coronary heart disease patient groups, one group receiving medical therapy alone, and the other group having circulatory surgery performed on them as well.

It should be stated that the work done in the field to date is only a start, an experiment, comparable to the first cholecystectomies or aortic aneurysm graft replacements; and with time, as in other, now tried surgical procedures, the risk will decrease and the successful results will probably increase. Finally, it should be remembered that the surgical approaches at revascularization utilized today are indirect ones, and do not attack the site of the disease, the coronaries themselves, for the standard approach to the heart would lead to fibrillation and death in a good percentage of the cases if the coronaries were themselves manipulated. It is, however, within the realm of realistic speculation that with the use of hypothermia and by-pass cardiac machinery, direct operative procedures—e.g., endarterectomy, graft replacement of a diseased segment, arterial graft to a coronary distal to an occlusive process—will be feasible operations in the not too distant future.

SUMMARY

1. The three leading surgical approaches to the revascularization of an ischemic myocardium are those of: a.) Beck: heart surface abrasion; insertion of coarsely ground asbestos; occlusion of the coronary sinus to 3 mm.; and application of the pericardium and mediastinal fat pad to the surface of the heart; b.) Thompson: insertion of magnesium silicate, a non-absorbable and irritating substance into the pericardial sac. c.) Vineberg: implantation of the left internal mammary artery into the left ventricle via a myocardial tunnel.

2. Noteworthy and provocative animal experiments to show the validity of revascularization procedures have been carried out by: a.) Beck, who has shown that his technique adds a flow of 4.7 c.c. of blood per minute to an ischemic area of myocardium, and that the quantity of backflow decreases the mortality in dogs whose coronaries were subsequently ligated; b.) Vineberg, who has demonstrated anatomically functioning vessels of arteriolar size between the coronary circulation and the extracardiac source, these anastomoses protecting the animal from a myocardial infarction post ligation of one of the major coronaries. He has also artificially recreated the gradual occlusive process of atherosclerosis, and by exercise tolerance tests has shown that animals receiving his procedure midway in their ischemic decline from normal tolerance regain most of their exercise potential, whereas the controls continue to lose their original exercise tolerance.

3. The human results of coronary heart disease surgery are promising: there has been a substantial decrease in the pain of angina pectoris, and an increase in the work capacity of the coronary heart disease patient; and there is some evidence that the eventual life expectancy of patients undergoing surgery has been increased.

4. It is evident that the greatest difficulty in justly appraising the benefits of surgery to the coronary heart disease patient is the lack of proper control series anywhere in the literature.

RESUMEN

1. Los tres métodos quirúrgicos principales para la revascularización del miocardio isquémico son: a) Beck: la abrasión de la superficie cardiaca; inserción de asbesto grueso; oclusión del seno coronario a 3 mm.; y aplicación del cojín grasoso pericárdico y mediastinal a la superficie del corazón; b) Thompson: insección de silicato de magnesio, substancia no absorbible e irritante, en saco pericárdico; c) Vineberg: Implantación de arteria mamaria interna izquierda dentro del ventrículo izquierdo por vía de un túnel en el miocardio.

2. Se han llevado a cabo experimentos notables y atrayentes en animales para mostrar la validez de los métodos de revascularización por: a) Beck que ha demostrado

que esta técnica agrega un caudal de 4.7 c.c. de sangre por minuto al área isquémica del miocardio y que la cantidad de reflujo decrece la mortalidad en los perros cuyas coronarias han sido ligadas después; b) Vineberg que ha demostrado la existencia de vasos anatómicamente capaces de funcionar de tamaño arteriolar entre la circulación coronaria y la fuente extracardiaca, siendo estas anastomosis las que protegen al animal del infarto cardiaco después de la ligadura de una de sus coronarias.

El, también ha vuelto a crear el proceso gradual oclusivo de la ateroesclerosis y por las pruebas de tolerancia del ejercicio ha mostrado que los animales sujetos a este procedimiento a mitad de la evolución de la declinación isquémica recuperan la mayoría de su potencial de ejercicio en tanto que los controles continuan perdiendo su tolerancia original al ejercicio.

3. Los resultados de la cirugía coronaria en los humanos es prometedora; ha habido un decrecimiento franco del dolor en la angina de pecho y un aumento en la capacidad de trabajo del enfermo con enfermedad coronaria; y hay alguna evidencia de que el término de vida de estos enfermos se alarga.

4. Es evidente que la mayor dificultad radica en la exacta estimación de los beneficios de la cirugía coronaria por la falta de series adecuadas de control en la literatura.

RESUME

1. Les trois tentatives chirurgicales essentielles qui permettent la revascularisation d'un myocarde ischémique sont celles de

a) Beck: abrasion de la surface cardiaque; insertion d'amiante grossièrement moulue; occlusion du sinus coronarien sur 3 mm.; et application du coussinet graisseux péricardique et médiastinal sur la surface du coeur;

b) Thompson: injection de silicate de magnésie, substance non résorbable et irritante dans le sac péricardique;

c) Vineberg: implantation de l'artère mammaire interne gauche dans le ventricule gauche par un tunnel myocardique.

2. Des expérimentations valables et pleines de promesse pour montrer la validité des moyens de revascularisation été menées à bien sur l'animal par:

a) Beck: qui a montré que sa technique ajoute un débit de 4,7 cc. de sang par minute à la zone ischémique du myocarde, et que cette quantité diminue la mortalité chez les chiens dont les coronaires ont été ligaturées ensuite.

b) Vineberg, qui a démontré l'existence de vaisseaux de la taille des artérioles, fonctionnant entre la circulation coronaire et la source extracardiaque, ces anastomoses protégeant l'animal d'un infarctus myocardique après ligature d'une des principales coronaires. Il a également recréé artificiellement le processus occlusif progressif de l'athérosclérose et par des tests de tolérance à l'effort, a montré que les animaux soumis à son procédé, regagnaient la plus grande partie de leur potentiel d'effort, tandis que les animaux témoins continuaient à perdre leur tolérance initiale à l'effort.

3. Les résultats de la chirurgie pour affection coronarienne sont prometteurs chez l'homme: diminution appréciable de la douleur dans l'angine do poitrine, et augmentation de la capacité de travail du malade atteint d'affection coronarienne. On a la preuve certaine que la survie des malades subissant cette chirurgie a été augmentée.

4. Il est évident que la plus grande difficulté d'apprécier à leur juste valeur les bienfaits de la chirurgie chez les malades atteints de maladie coronarienne est due à l'absence de cas sérieusement contrôlés dans la littérature.

ZUSAMMENFASSUNG

1. Die drei Hauptsächlichen chirurgischen Wege für die Revascularisierung eines ischaemischen Myocards sind diejenigen von:

a) Beck: Abrasio der Herzoberfläche; Aufbringung von grobkönig grundiertem Asbest; Verschluss des Coronarsinus bis auf 3 mm; Anheftung des pericardialen und mediastinalen Fettlagers an die Herzoberfläche;

b) Thompson: Aufbringung von Magnesiumsilikat, einer nicht absorbierbaren und reizenden Substanz in das Innere des Herzbeutels.

c) Vineberg: Implantation der linken art. ham. int. in den linken Ventrikel mittels eines Tunnels durch das Myocard.

2. Bemerkenswerte und anregende Tierversuche, um den Wert der Methoden der Revascularisierung zu demonstrieren, sind ausgeführt worden von: a) Beck, der nachgewiesen hat, dass durch seine Technik einem ischaemischen Bezirk des Myocards eine Durchströmung von 4,7 ccm Blut pro Minute zugeführt wird und dass das Ausmass des Rückflusses die Mortalität von Hunden verringert, deren Coronararterien anschliessend unterbunden wurden; b) Vineberg, er wies anatomisch funktionierende Gefässe von der Grössenordnung von Arteriolen nach zwischen dem coronaren Cirkulationssystem und der extracardialen Quelle, wobei diese Anastomosen das Tier vor einem Myocard-Infarkt bewahrten nach Ligatur einer der grösseren Coronararterien.

Er hat auch auf künstlichem Wege den Prozess des schrittweisen Verschlusses, der Atherosklerose entsprechend, hervorgerufen, und bei Belastungsproben zeigte er, dass Tiere, an denen sein Verfahren angewandt worden war, auf halbem Wege zu ihrem ischaemischen Verfall von normaler Verträglichkeit den grössten Teil ihres Belastungs-Potentials wiedererlangen, wo hingegen die Kontrolltiere fortgesetzt die ursprüngliche Belastungstoleranz weiter verlieren.

3. Die Ergebnisse am Menschen mit Operation wegen Herzkranzgefässerkrankung sind vielversprechend. Es kam zu einer beträchtlichen Abnahme im Schmerz der Angina-pectoris und zu einer Zunahme der Arbeitskapazität der Patienten mit Herzkranzgefäss-Erkrankung; und es liegen Anhaltspunkte dafür vor, dass sich die mögliche Lebenserwartung von chirurgisch behandelten Fällen erhöht hat.

4. Es liegt auf der Hand dass die grössten Schwierigkeiten bezüglich einer direkten Abschätzung der Vorzüge der chirurgischen Behandlung von Patienten mit Herzkranzgefäss-Erkrankung darin liegen, dass überall in der Literatur eine angemessene Kontrollserie fehlt.

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The Problem of Surgery of the Aortic Valve

It is of historic interest that when, in 1912, Theodore Tuffier[1] operated upon a young man for aortic stenosis, his original intention was to incise the valve with a knife through a supravalvular approach, but he decided that there was not enough experimental observation to justify the attempt and instead dilated the valve by digital invagination of the aortic wall into the valvular orifice. For the next 35 years, little was accomplished towards the solution of the problem of aortic valvular surgery. Horace Smithy's untimely death halted his experiments on excision and replacement of excised valve cusps in dogs.[2] Within a year, in 1949, Charles Bailey began an all-out assault on the problem. He recognized "the tendency of the stenotic aortic valve to split preferentially along the lines of the commissural fusion"[3] an observation that became the basis for all dilating types of aortic valvular surgery. During the next few years, instruments for transventricular dilation of aortic stenosis were developed by Bailey[4] and Brock.[5] The surgical mortality was high and so the supravalvular aortic approach was developed by Bailey[6] in 1952 using a pouch of pericardium sutured to the lips of an incision made in the ascending aorta. To instrumental dilation, direct palpation, finger fracture and incision were added by Bailey and Harken.[7] Swann et al.[8] utilized artificial appendages made of latex and plastic sewed on to the ascending aortic arch, and Goldman employed simple commissurotomy through a 1 cm. aortic incision using special, sharp, light, bent valvulotomes, in 12 patients with far advanced calcific stenosis.[9]

Once the supravalvular approach was accepted, the way was open to the development of direct vision surgery, and so under hypothermia and inflow occlusion, Lewis[10] and Swan[11] were able to achieve better correction of the gradient across the valve. Lillehei first[12] then Bailey[13] and Morrow[14] undertook direct surgery upon the valve using an open technique and a heart-lung bypass. Subsequently Bailey[15, 16] utilized direct cannulation of the coronary arteries for perfusion of the myocardium with oxygenated blood during the bypass. Because of the relatively long time required for the surgery Blanco developed the technique of employing the patient's own lungs for oxygenation while using two pumps to replace the ventricles. Glover[17] and Brock[5] continued to advocate transventricular dilation because of the initially lower surgical mortality. Many cardiologists continued to be reluctant to refer patients with aortic valvular disease for surgery because long term results were not yet entirely satisfactory and because of the belief that adequate restoration of valve function could not be obtained. Hope was expressed that an artificial valve placed at the natural aortic valve level with or without total removal of the diseased valve would be the answer. In the past few

months, two patients had soft silastic plastic valves inserted by Lillehei.[18] Byron and Fields[19] recently have placed hard plastic valves just above the coronary sinuses in dogs. The long term tolerance of such hard plastic and silastic valves has not yet been established.

Thanks to the efforts of our medical colleagues, we now have available physiological methods of assessing the pressure gradient between the left ventricle and the aorta by left heart catheterization. Calculations of cardiac output and aortic valve size, and of regurgitant blood volume, taken together with data from the more commonly employed clinical examinations make possible an assessment of the valve to form a baseline for postoperative evaluation of the surgical results. These data also serve as prime indications for surgery.

Now, in the past two years the problem has become more clearly defined as the pathophysiology is seen at operation and can be measured in the living patient. It is no longer enough to consider the relief of aortic stenosis as accomplished by simply dilating the stenotic orifice or by splitting one or two commissures. In addition to relieving valvular obstructive elements, total correction of the gradient across the valve, reduction of any regurgitant aspects and restoration of cardiac output are more within our grasp. Great restoration of the disturbed hemodynamics is now possible.

The major pathology affecting the aortic valve can be surgically corrected without inserting foreign materials likely to be troublesome in the future. Coronary perfusion added to total body perfusion with the aid of a pump oxygenator or by means of an autogenous lung to substitute for the oxygenator offers time for prolonged plastic sculpturing of the calcifically deformed valves to restore flexibility to valve cusps. Techniques to convert the incompetent tricuspid aortic valve into a competent bicuspid one in humans have been described separately by Lillehei,[12] by Creech,[20] by Cooley,[21] by Bailey[15, 16, 22] in 60 patients, and by Garamella[23, 24] in dogs. We[25] have successfully performed a new type of bicuspidization operation employing a free autogenous arterial graft to reinforce the sutured commissure with apparent complete correction of marked incompetence. A pump oxygenator was used during the 30 minutes of cardiac bypass with coronary perfusion while the aortic valve was completely visualized in a dry field.

The safety of extracorporeal and coronary perfusion methods is increasing rapidly; in contrast to the continued occurrence of death in a large percentage of patients even while they are awaiting recommended surgery. The pessimism of the past regarding aortic valvular surgery should give way to an optimistic clinical trial of these newer methods since they are designed for complete correction of valve function, an objective not previously attainable.

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References will appear in author's reprints.

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ELECTROCARDIOGRAM OF THE MONTH

Electrocardiographic Artefacts

This tracing was obtained on a 56 year old patient. The interesting arrhythmia which is best recognized in the limb leads very closely mimics that of auricular flutter. However, the value of the tracing lies in the fact that the patient had no heart disease, but the base line disturbance is due to paralysis agitans: Parkinson's tremor. The amplitude of the chest leads is decreased; however, note that the chest leads have been recorded half standard.

An oscillating electrical fan, the ringing of a telephone, the electrical disturbance from overhead fluorescent lights, the ringing of a buzzer, these all can produce regular electrical disturbances in the base line.

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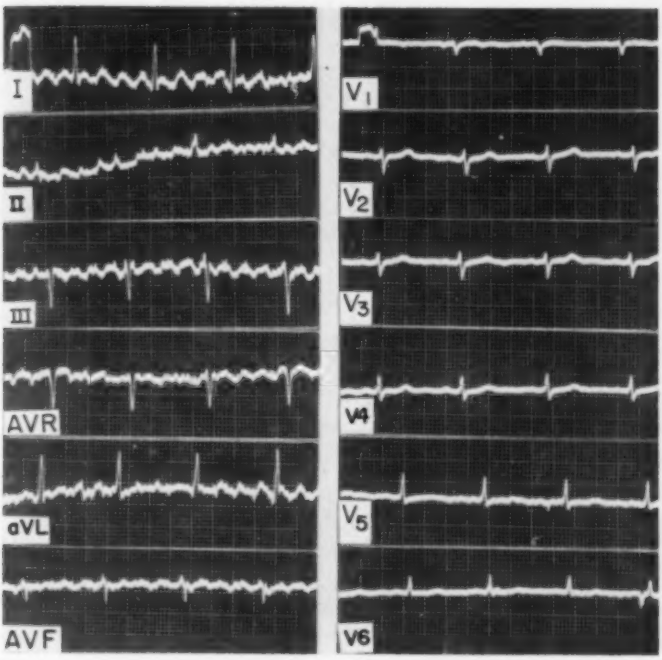
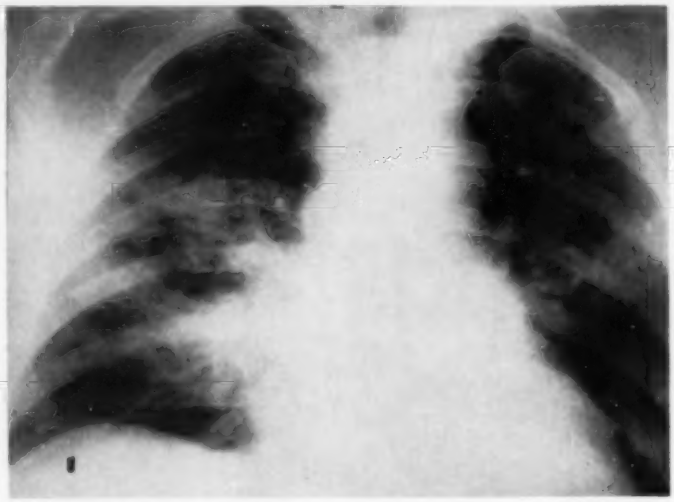


X-RAY FILM OF THE MONTH

Clinical Information

White man, age 59, entered the hospital with a huge chronic progressive ulceration of his left thigh which began about July, 1953. This was accompanied by low grade fever and weight loss. All laboratory studies, including skin tests and cultures, were non-revealing except for eosinophilia of 10 to 15 per cent. Biopsy of the thigh showed granulomatous fat necrosis. All therapeutic measures failed to control the lesion. Dyspnea appeared in December, 1953, and became progressively worse. Bronchoscopy revealed edema and ulceration in several of the large bronchi. The film below was obtained in January, 1954. The patient expired two weeks later.



ANSWER

Wegener's Syndrome

Falling into the general category of non-infectious necrotizing granulomatosis, Wegener's syndrome is basically characterized by three features: necrotizing granulomatous lesions of the upper or lower respiratory tract or both, glomerulitis, and disseminated arteritis similar to that of periarteritis nodosa. Not all features need be present to establish the diagnosis. Related, yet exhibiting certain differences, are Churg and Strauss' granulomatosis and midline lethal granuloma.

Peak age incidence is in the fourth and fifth decades. An allergic history is frequently elicited. The respiratory tract is often the site of the initial symptomatology. There may be persistent rhinitis or sinusitis which may progress to severe destruction of the midline structures of the face. Extensive granulomas of the skin occasionally occur, as in the present case. Pulmonary involvement is heralded by cough, hemoptysis, dyspnea, and chest pain. Signs and symptoms of renal disease develop later in most of the cases. Uremia is the most common mode of death. Hypertension is

not common. Constitutional manifestations such as persistent fever, weight loss, and weakness will, on occasion, be out of proportion to the local symptoms. Anemia, leukocytosis, eosinophilia, and increased sedimentation rate are often present. Almost every organ in the body can be involved by either the granulomatous process or the arteritis. Bacteriological study has been noncontributory.

Positive roentgen findings associated with involvement of the facial area include sinusitis and destruction of bone. Tomography may demonstrate laryngeal or tracheal lesions. The findings in the chest, although nonspecific, are extremely helpful in the diagnosis. Solitary or multiple nodules or infiltrates of chronic nature with central cavitation may occur, as in the present case. These roentgen findings, along with the previously described clinical picture, should suggest the diagnosis.

Almost all cases thus far reported have terminated fatally within six months to two years. No effective treatment has been found.

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Case Report Section

Aneurysmal Venous Dilatation in Marfan's Syndrome*

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Since the original description of Marfan's syndrome in 1896, over 350 cases have been reported in the literature.[1] It has been accepted as an hereditary disorder of the connective tissue with widespread malformations of the musculoskeletal, the cardiovascular, and the ocular systems.[2] The exact etiology and pathogenesis is not known. Of special interest is the experimental production, in rats fed Lathyrus odoratus seeds, of musculoskeletal and cardiovascular changes similar to those seen in patients with Marfan's syndrome.[3-5] A variety of manifestations associated with this syndrome have been reported. The most common ones are the following:

I. Musculoskeletal system: Dolichostenomelia, dolichocephaly, high arched palate, cleft palate, pectus excavatum, pectus carinatum, kyphoscoliosis, spina bifida, hemivertebra, winged scapula, hyperextension and subluxation of joints, pes planus, hernia, muscular hypotonia.

II. Cardiovascular system: Diffuse aneurysm of aorta, dissecting aneurysm of aorta, coarctation of aorta, aneurysm of innominate and common carotid arteries, patent ductus arteriosus, dissecting aneurysm of pulmonary artery, congenital and idiopathic dilatation of pulmonary artery, involvement of the semi-lunar valves, aneurysmal dilatation of aortic sinuses of Valsalva, involvement of atrio-ventricular valves and chordae tendinae, patent foramen ovale, interatrial septal defect, tetralogy of Fallot, and varicose veins.

III. Ocular system: Ectopia lentis, coloboma of lens, retinal detachment, abnormalities of lens and cornea (microphakia, spherophakia, megalocornea, microcornea, keratoconus).

IV. Pulmonary system: Susceptibility to respiratory infections, developmental malformations of the lung, cystic disease of lung, spontaneous pneumothorax.

V. Renal system: Ectopic kidney with hydronephrosis, polycystic kidneys, atresia of the ureter.

This paper reports a case of Marfan's syndrome with aneurysmal dilatation of a neck vein, venous varicosities, intractable stasis ulcer of the leg, testicular atrophy, and other more commonly seen abnormalities.

Case Report

V. R. No. 891028. A 42 year old farmer was hospitalized from November 23 to December 23, 1955, because of severe congestive heart failure, a mass in the right supraclavicular fossa, and intractable leg ulcer. He first knew he had some difficulty with his heart when in 1940 he was rejected from military service because of a heart murmur. Prior to 1949, he was engaged in heavy farm work with no symptom. In 1949 his heart was apparently fibrillating and he was treated with digitalis and bed rest. He improved in about two weeks and has been on digitoxin (0.15 mg. daily)

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since that time. He had not worked much for the past four years because of intermittent bouts of congestive heart failure. About four weeks prior to admission his symptoms gradually increased. He developed paroxysmal nocturnal and marked exertional dyspnea, retrosternal pain coming upon exertion, and increasing peripheral edema. Three months prior to admission, during an episode of cardiac decompensation, he noticed a swelling in the right supraclavicular fossa, about the size of a tennis ball. This mass would become more marked on exertion, talking, lying down flat, coughing or sneezing. There was no pain associated with the mass, but there were pressure symptoms manifested primarily as a choking sensation in "getting in breath" ("seems to shut off my breath in one side").

His past history was significant in that at age six he had acute tonsillitis and tonsillectomy followed by Sydenham's chorea and an ill-defined illness of one year. There was no history of joint and cardiac involvement. About four months prior to admission he developed an ulcer on his right leg which seemed to heal for a few days to break open again later. He was never married and apparently had never had sexual intercourse or masturbated. Family history revealed that the immediate members of his family, including the parents and six brothers and five sisters, were of average body build. There was no history of cardiovascular disease in the family except for the mother who had high blood pressure. Two sisters and three children (out of five examined) of these two sisters had skeletal abnormalities such as pigeon breast, high arched palate, kyphoscoliosis, arachnodactyly and pes planus. Cardiac examination including electrocardiograms and cardiac fluoroscopy was normal.

Physical examination on admission revealed a tall slender man who appeared chronically ill. There was mild cyanosis of lips. He was 74¼ inches tall and weighed 180¼ pounds. Fingertip-to-fingertip span was 78 inches and pubic symphysis-to-heel dimension was 41¼ inches (over half his total height).

The extremities including the phalanges were long and thin. There was marked arachnodactyly of fingers and toes and bilateral pes planus. The palate was high-arched and the auditory canals were wide and very short. Both ears were long and pointed. The nasal passages were narrow. There was moderate kyphoscoliosis of the thoracic spine. The left hemithorax was slightly larger than the right one. There was a nontransluminant cystic mass, about the size of a tennis ball in the right supraclavicular fossa (Fig. 1). This mass could be reduced by gentle pressure while the patient was in a sitting position. There was a fine intermittent thrill and a to-and-fro bruit of the venous hum type at the lower and medial extremity of the mass, but there were no intrinsic pulsations. There were venous varicosities in the right lower leg and a 1.5 cm. round, punched-out right pretibial ulcer that extended to the periosteum. This was surrounded by a pigmented indurated area. There was a two plus bilateral leg edema. The blood pressure was 138/72, the pulse irregular, and the temperature 96.60°F. The heart was enlarged both to the left and to the right. The point of maximum cardiac impulse was at the left anterior axillary line in the fifth

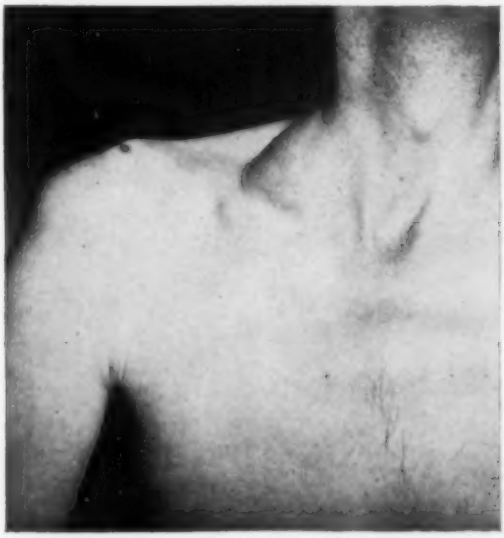

FIGURE 1: Venous aneurysm in the right supraclavicular fossa

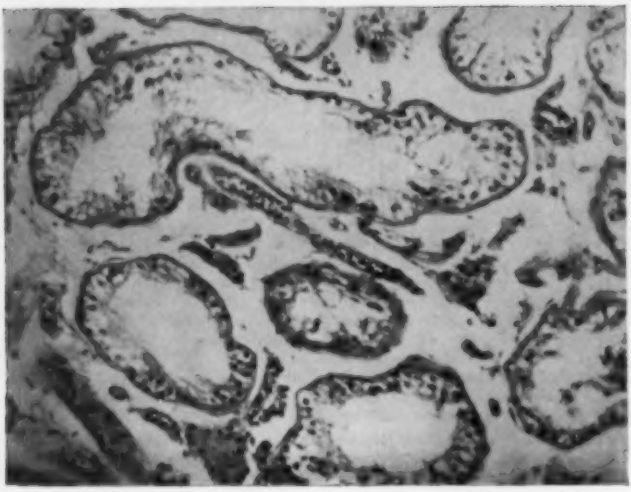

FIGURE 2: Photomicrograph, testicular biopsy (X 175).

intercostal space. The left border of the cardiac dullness extended 3 cm. to the left of the anterior axillary line, and the right border was 4 cm. to the right of the sternum in the fourth intercostal space. The rhythm was irregular. There was a systolic thrill and a grade III systolic murmur at the apex which was transmitted to the left axilla. The first mitral sound was not accentuated. In addition, there was a grade IV harsh systolic murmur over the third intercostal space, at the left sternal border. P^2 was louder than A^2. There were rales in both lung fields posteriorly. The liver was pulsatile and was four finger breadths below the right costal margin. Examination of the abdomen was otherwise negative. The penis was small and the testes were mushy and atrophic. The hair distribution appeared normal. Verbal scale I.Q. was found to be 77. Laboratory studies including red-cell and white-cell counts, hemoglobin, erythrocyte sedimentation rate (Westergren), blood urea nitrogen, glucose, electrolytes, basal metabolic rate, protein bound iodine, urinary excretion of follicle-stimulating hormone, and blood Kline test were within normal limits.

Urinalysis revealed one plus albumin and occasional red cells. The 24 hour urinary 17-Ketosteroid excretion was 4.9 mg. (N: 10-24 mg.). The venous pressure was 23.5 cm. citrate and the arm-to-tongue circulation time was 65 seconds. Needle aspira-

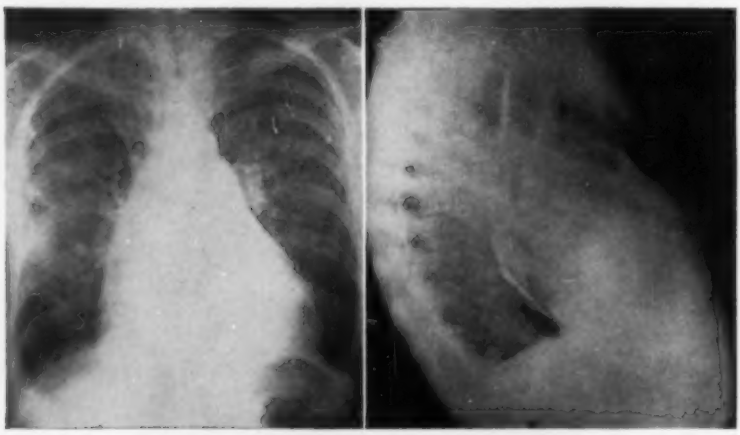

FIGURE 3A FIGURE 3B

Figure 3A: Frontal teleroentgenogram.—*Figure 3B:* Right anterior oblique view.

tion of the mass in the neck yielded dark red blood and there was no external distortion on gentle rotation of the needle through a wide arc. The oxygen saturation of this blood was 57.6 per cent, that of the right arm vein 55.5 per cent and the femoral artery blood 96.6 per cent. Biopsy specimens (Fig. 2) obtained from both testes revealed the seminiferous tubules to be completely lacking in spermatogenic cells. Interstitial cells were present and appeared normal. In some of these cells ceroid pigment was found. Electrocardiograms showed atrial fibrillation numerous ventricular extrasystoles from multiple foci, right axis deviation and right ventricular hypertrophy. Cardiac catheterization done on December 6, 1955, showed a pulmonary artery pressure of 87/42 mm. Hg, a right ventricular pressure 86/9 mm. Hg, and a right atrial mean pressure of 10 mm. Hg and no evidence of intracardiac shunt. Angiocardiography done at the same time did not reveal shunts at either the atrial or the ventricular level. Cardiac fluoroscopy showed generalized cardiomegaly with right and left ventricular enlargement and slight left atrial enlargement. No calcifications were seen. In addition, there was basilar emphysema and poor motion of the diaphragms. Postero-anterior and lateral chest X-rays revealed marked cardiomegaly with apparent generalized enlargement (Fig. 3). Both hilar shadows were prominent. There was rather marked pulmonary congestion and edema, granular appearance throughout both lungs, and considerable basilar emphysema. There was a large soft tissue mass in the lower neck on the right side. In addition there was marked degree of kyphosis of the dorsal spine. X-rays of the esophagus, stomach, duodenum, and intravenous pyelograms were negative. Barium enema showed several diverticula of the sigmoid colon.

He was treated with low sodium diet, oral potassium chloride (2 grams three times daily), oral pronestyl (250 mg. four times daily) and parenteral mercurial diuretics. Digitoxin was discontinued. On this regimen, the patient showed improvement. The ectopic beats disappeared and he lost 20 pounds in the first week. After his general condition improved the mass in the right neck disappeared completely, and the chest X-rays revealed marked reduction in heart size and considerable clearing of the congestion and of the granular appearance of the lungs. He was discharged from the hospital on December 23, 1955 on a maintenance dosage of digitalis. The stasis ulcer showed some improvement on conservative treatment, but did not heal completely. During 1956, he was admitted to the hospital three more times, each time in congestive heart failure. During each admission the large mass in the right fossa supraclavicularis would become prominent to disappear completely upon correction of the congestive heart failure. The leg ulcer persisted as an intractable stasis ulcer although there was marked reduction in its size.

DISCUSSION

This man has many of the characteristic clinical features of Marfan's syndrome which permit diagnosis at a glance. Ocular abnormalities which are seen in up to 75 per cent of cases having this syndrome[7, 16] are absent in this case. The cardiovascular system involvement which is seen in 30 to 60 per cent of cases[7, 16] appears to be limited to heart and veins. Aorta, pulmonary arteries, and the other major arteries are grossly normal. The main lesion in the heart appears to consist of mitral valvular disease with mitral incompetence. The pulmonary hypertension and the left and right heart failure are most likely secondary to mitral incompetence. There were no intracardiac shunt demonstrable by cardiac catheterization or angiocardiography.

It is not possible to tell whether the mitral lesion was due to rheumatic valvulitis or to noninflammatory process as often seen in Marfan's syndrome. It has been shown that the main valvular changes in Marfan's syndrome consist of thickening and shortening of valves and the chordae tendinae and microscopically the lesions have been described as being of a fibromyxomatous character.[7-9] There is a high incidence of aortic involvement in this syndrome. The nature of aortic lesions has been well outlined.[2, 7, 10-14, 16] Cases of Marfan's syndrome have been reported with death due to dissecting aneurysm of the aorta developing after trauma.[10, 12] The unusual hazards of trauma in this condition have recently been emphasized.[15] Rupture of aortic valves and death due to dissecting aneurysm of innominate and carotid arteries have also been reported.[6, 17, 18]

Several authors[2, 5, 19] have mentioned the association of varicose veins and varicose ulcers with Marfan's syndrome; however it is not possible from the reported cases, to get an exact idea about the incidence of venous anomalies in this condition. It has been assumed that the loss of the subcutaneous support to the veins encourages the production of varicosities and intractable varicose ulcers.[5] The large aneurysmal venous dilatation in the right supraclavicular fossa of this patient is an interesting finding. To our knowledge, this type of venous anomaly has not been reported in Marfan's syndrome. From the behavior of this mass, one is forced to conclude that it is probably due to weakness affecting the connective tissue and the vascular wall. It is interesting to note that this mass becomes largest at the height of congestive heart failure when the venous pressure is elevated and disappears completely after the patient improves.

From the reported cases one gets the impression that patients with Marfan's syndrome do not have abnormalities referable to their sexual organs. The case reported here has severe testicular atrophy and sexual impotence.

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Atypical Pneumonitis with Interstitial Fibrosis: An Unusual Case Receiving Prolonged Corticosteroid Therapy*

Pulmonary Alveolar Proteinosis

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Recently Rosen and coworkers[1] reported an unusual histologic pattern in the lungs consisting of alveolar deposition of a granular proteinoid material. They designated their findings as "pulmonary alveolar proteinosis." These changes were found in biopsy or autopsy specimens of the lung which were referred primarily for tissue diagnosis. One of these patients was under our care. Since their description is primarily pathologic, and because our patient was under prolonged, close clinical observation, it is considered worthwhile to present this case in detail.

Case Report

A white, electrical appliance repairman, aged 35 years, was admitted to the hospital on March 9, 1956, for evaluation of an abnormality detected on a chest roentgenogram from a mass survey unit in January 1956. He dated his illness to June 1955, when he had multiple alveolar abscesses and underwent extractions of the upper teeth. His weight declined from 165 pounds in the summer of 1955 to 138 pounds by Christmas 1955.

In December, 1955, he had an illness, diagnosed as pneumonia, which consisted of fever, pain in the chest, cough, malaise, and muscular aches. He was treated with sulfa drugs and penicillin. He returned to work in six days but did not feel as well as prior to his illness; also, he noticed dyspnea on exertion. He had no current symptoms of orthopnea, paroxysmal nocturnal dyspnea, wheezing, pedal edema, known allergy, chills, pleuritic pain, or expectoration. He did have a chronic cough, however, aggravated by

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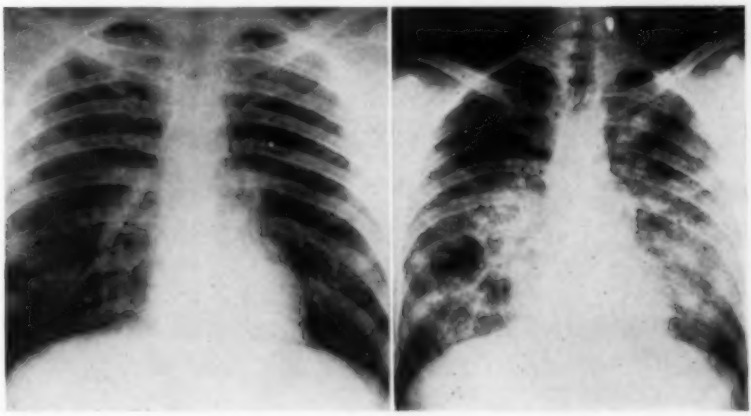

FIGURE 1: Normal chest x-ray on left, taken 1950. Film on right taken on admission to hospital 1956.

cigarettes, but this was essentially non-productive and unchanged from what it had been through the years. He smoked one package of cigarettes daily.

As a result of wartime service in the Pacific, he suffered a missile wound to the jaw and throat with subsequent osteomyelitis of the mandible. He gave no history of exposure to insecticides or contact with pets, farm animals or animal quarters. He had questionable exposure to broken fluorescent bulbs.

Systemic review revealed the presence of indigestion and heartburn of one year's duration. The symptoms were relieved by "Tums" or milk and were unrelated to specific foods.

On *physical examination*, he was well developed and well nourished and did not appear ill. Deformity of the left mandible from the previous injury and osteomyelitis were noted. Questionable dullness was present over the right lung base posteriorly and in this area there was slight decrease in tactile fremitus and slight decrease in breath sounds. Scattered throughout both lungs, particularly in the basilar portions, were terminal expiratory fine rales, cleared by coughing. No wheezing was present. Blood pressure was 118/76 mm. of mercury. A_2 was equal to P_2. No abdominal organs or masses were palpable. Lymphadenopathy was not present.

Laboratory examinations. Upon admission, the white blood cell count was 6,800 per cu. mm. with a normal differential blood smear; hemoglobin was 17.6 Gm. per 100 ml. and the hematocrit was 51 per cent. Sedimentation rate (Wintrobe) was 13 mm. in one hour. Urine specimen was normal. Serologic tests for syphilis were negative. Sputum smears and cultures of 72-hour specimens were negative for acid fast bacilli. Serum calcium and phosphorus determinations were 9.9 and 3.9 mg. per 100 ml. respectively. Alkaline phosphatase (Bodansky method) was three units per 100 ml. Serum albumin was 4.7 Gm. per 100 ml. and globulin was 2.0 Gm. per 100 ml. Electrocardiogram was within normal limits. Pulmonary function studies showed a moderate restrictive defect.

Chest roentgenograms on admission showed a fine granulomatous type of infiltration with a tendency to confluency. This infiltration was scattered throughout the left and the lower two thirds of the right lung (Fig. 1). A normal chest roentgenogram of March 9, 1950, was available for comparison. Planigrams did not show evidence of cavitation or significant hilar adenopathy.

Course in the Hospital. At the time of admission, he was relatively asymptomatic, although he did complain of some shortness of breath. He had been afebrile and his weight had been steady. In view of the paucity of symptoms, together with the rather striking bilateral pulmonary infiltrate, a diagnosis of sarcoidosis was considered. A supraclavicular biopsy on April 3, 1956, showed normal tissue. On April 16, 1956, an exploratory thoracotomy with biopsy of the lung was performed.

The findings at operation showed some filmy adhesions between the anterior and

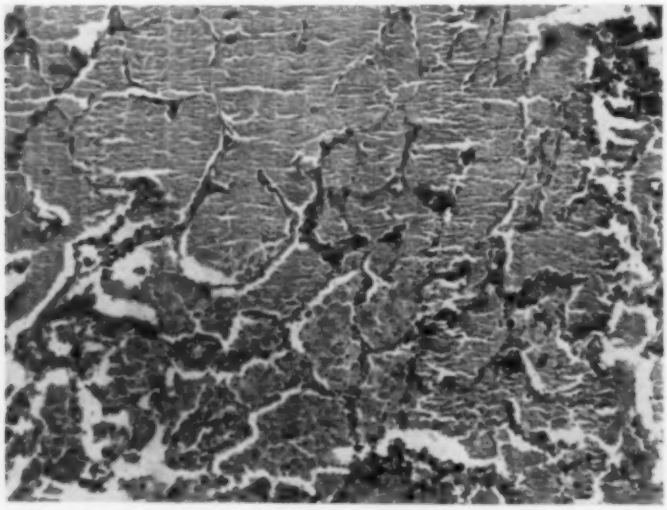

FIGURE 2: Lung biopsy (68X) showing pink-staining material in some alveoli and foamy histiocytes in others. Interstitial fibrosis is present in some areas but is not prominent.

posterior segments in the right upper lobe to the chest wall. The entire right lung, especially the lower lobe and anterior segment of the right upper lobe, had fine nodularity and various degrees of thickening and nodules measuring from fine seeds to several cm. in diameter. In some areas, these were subpleurally located. The lung did not exhibit normal resiliency and crepitation. The hilum was normal. No enlarged nodes were visible.

Microscopically (Fig. 2), the striking feature was deep pink-staining material filling the air spaces. Many of the air spaces were slightly, but uniformly, distended, and the adjoining septae were not remarkable. In the mid-lateral aspects, surrounded by the areas described above, were air spaces containing moderate numbers of foamy histiocytes and the neighboring septae were thickened slightly, and the alveolar lining cells were moderately prominent. Small groups of air spaces contained both the pink-staining material and foamy histiocytes. Special staining procedures revealed normal findings (Sudan IV, crystal violet, congo red, mucicarmine, alcian blue). Smears and cultures for bacteria (aerobes and anaerobes), fungi and acid fast bacilli were negative. Granuloma or foreign material such as asbestos were not seen. The slide was interpreted to show: 1) Unidentified intra-alveolar material, and 2) Pulmonary fibrosis (slight).

Following the lung biopsy, a chest roentgenogram showed some increase in the diffuse infiltrate. Liver function studies at this time showed a normal bilirubin; thymol turbidity of 6.7 units and cephalin flocculation of 3-plus in 48 hours. Corticosteroid

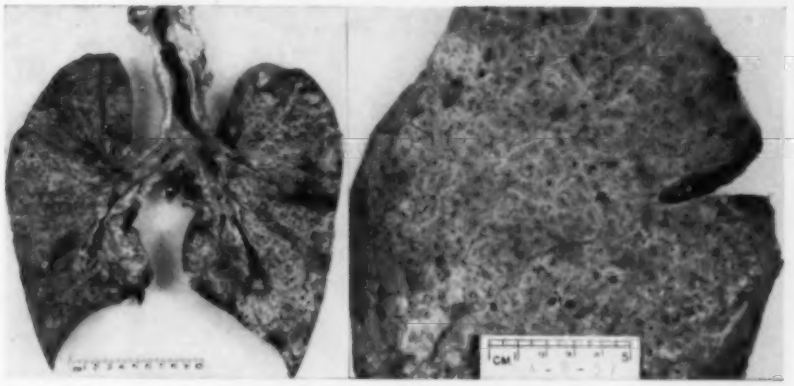

FIGURE 3: Gross appearance of lung at autopsy. Lung sectioned (at left) showing diffuse involvement.

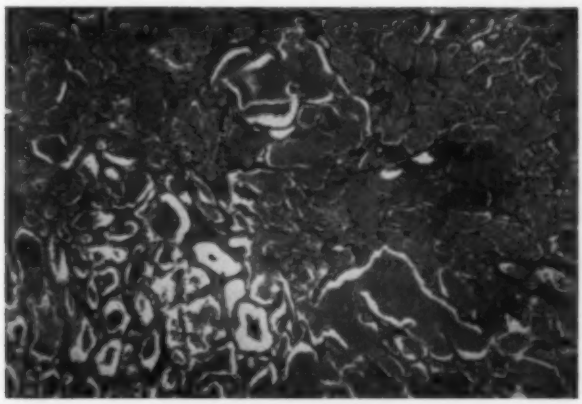

FIGURE 4: Photomicrograph (26x). Section of lung at autopsy showing three main pathologic features (1) pink-staining material in alveoli in central area, (2) alveoli filled with foamy histiocytes (upper right), and (3) moderate interstitial fibrosis (lower left).

therapy in the form of prednisone (50 mg. a day in four equally divided and equally spaced doses) was started on May 21, 1956. On June 25, he complained of nervousness, easy fatigability, and sensations of fever. Temperature of 100° F. was documented; he had purulent sputum and was cyanotic. Laboratory examinations then showed a red blood cell count of 6.7 million per cu. mm. with a hemoglobin of 17.8 Gm. per 100 ml. and hematocrit of 57 per cent. White blood cell count was 14,700 per cu. mm., with 81 per cent polymorphonuclear neutrophils, 13 per cent lymphocytes and 6 per cent monocytes. Platelets were 366,000 per cu. mm.

Because severe secondary infection was thought to be present, the dose of prednisone was gradually reduced. By July 8 it had been decreased to 15 mg. a day. On July 3 he had been placed in an oxygen tent because of cyanosis. On July 10 it was noted that he was markedly cyanotic even while in the oxygen tent. On July 13 prednisone was increased to 20 mg. a day. By July 25 he appeared slightly improved and less cyanotic. By August 8 he was out of the tent for short intervals. Chest roentgenogram on August 20 showed some clearing of the bilateral infiltrate. By August 27

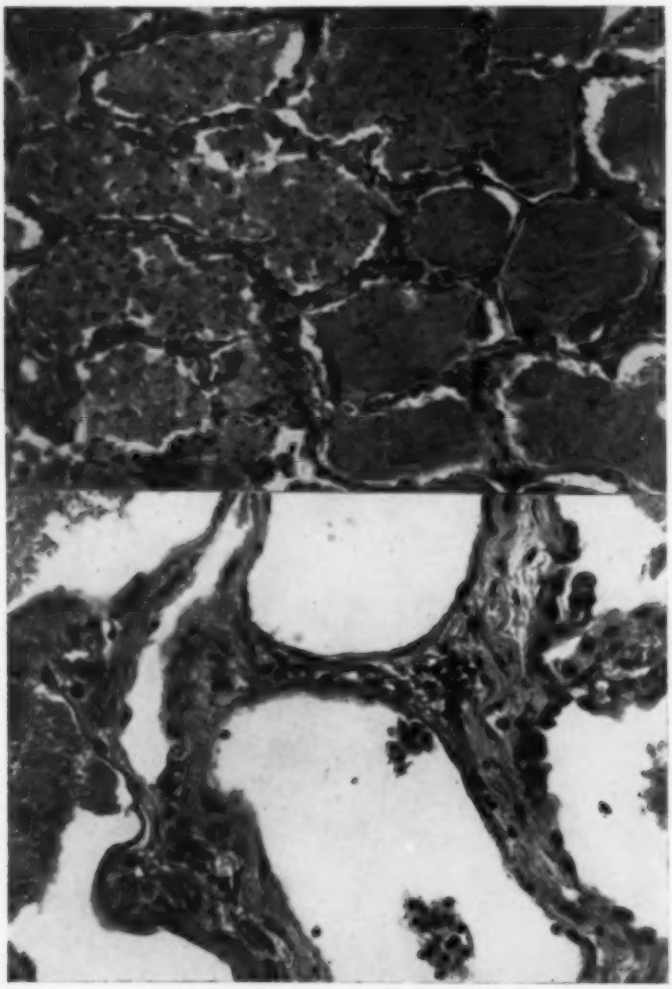

FIGURE 5

FIGURE 6

Figure 5: Higher power (112X) of part of field seen in Fig. 4, showing pink-staining material in some alveoli and foamy histiocytes in others. Note the slight fibrous thickening of the septae.—*Figure 6:* Autopsy section of lung (244X) showing fibrous thickening of alveolar septae and pronounced alveolar lining cells.

he was out of the oxygen tent up to 10 minutes. During the period from July 13 to October 23, the dose of prednisone was 20 mg. daily.

On August 30, the left mandible had some swelling at the angle and an abscessed tooth was removed. On September 7, he had incision and drainage of the left mandible at the angle. About this time, he was able to get out of the tent for up to 20 minutes, four or five times a day; and he was sitting in a chair for 15 minutes, two or three times a day. He had gained about three or four pounds in weight. On October 10 he had another flare-up of osteomyelitis with drainage from the jaw, and he became more dyspneic. He was unable to be out of the tent more than 10 or 15 minutes at a time. On October 23 the dosage of prednisone was increased to 30 mg. a day. By November 22 he was short of breath and cyanotic even in the oxygen tent. On December 5 corticosteroids were increased to 40 mg. a day. A week later he had slight mental aberrations. The dosage was cut to 35 mg. daily, and the mental symptoms seemed to improve. His condition continued to deteriorate and by January 18, 1957, he was receiving 45 mg. of corticosteroids daily. By January 25 he was alternately comatose and conscious. On February 2, 1957, he expired.

Additional laboratory and clinical data. During his entire stay in the hospital from May 1956 until death in early February 1957, this patient was on continued antibiotic therapy with most of the known antibiotic agents being given in full therapeutic dosages at one time or another. Beginning in September the chronic infection in the left jaw necessitated three or four procedures for incision and drainage. During the last month of his life, discharge was minimal. Cultures from the jaw were negative for anaerobic organisms and aerobic cultures showed a light growth of coagulase negative Staphylococcus aureus. Cultures on Sabouraud's medium were negative.

Blood pressure was stable throughout his hospital course. He had a slight cough, usually non-productive. The slightest exertion, even while in the tent, produced shortness of breath. In July, the second pulmonic sound became markedly accentuated and was louder than the aortic second sound. Scattered throughout both lung fields were small fine, moist inspiratory rales, more prominent over the lower portions of the chest, bilaterally.

During hospitalization, he received other medications in addition to the corticosteroids and antibiotics. These included small amounts of antacids and therapeutic vitamins, plus continuous oxygen in the tent. With the oxygen, he had a combination of Isuprel (1:200) and Alevaire in a mixture of 1:5, respectively, administered by a Mist-O$_2$-Gen nebulizer for four hours and then omitted for four hours.

Blood electrolytes ranged within normal limits except for the serum bicarbonate which was elevated to 30-36 milliequivalents per liter during the last two weeks of his life. Serum globulin values never were elevated. Liver function studies in January 1957 were normal. After June 1956, white blood cell counts were consistently elevated to as high as 25,000 per cu. mm., and one before death was 50,000 per cu. mm.; differential blood smears showed increased polymorphonuclear neutrophils without eosinophilia. Blood morphology was not remarkable. Smears of peripheral blood for lupus erythematosus cells (LE preparation) were negative on two occasions.

About 12 days before death, he developed fever and his pulse rate rose to levels of 120 to 140, having previously varied from 80 to 130 per minute, with an average range of 90 to 110.

At autopsy (Fig. 3), the lungs weighed 3100 Gm. A few fibrous pleural adhesions were present over the right upper lobe area. The lungs were non-crepitant. A few distended air spaces were present in the upper portions of both upper lobes. In the lateral and medial aspects of the lower lobe of the right lung were a few cysts, ranging in diameter from 3 to 12 mm. The remaining cut surface was dry, grey-white, firm, nodular and mottled. In the lower medial aspect of the upper lobe of the left lung, was an abscess measuring 5 cm. and containing about 30 cc. of turbid, green-yellow fluid. Bacteriologic studies of the fluid (including fungus studies) were negative. The bronchial system, the pulmonary arterial and venous trees, peribronchial and tracheo-bronchial lymph nodes were not remarkable.

Microscopically, all sections showed a similar pathologic process. The main features were similar to the lung biopsy; intra-alveolar deposition of a proteinoid material, interstitial fibrosis, prominent cells lining the alveoli, and large numbers of foamy macrophages (Figs. 4 and 5). Fibrous thickening of the alveolar walls was slight to moderate and in some areas the interstitial fibrosis was quite severe (Fig. 6), particularly in those areas where more of the pink proteinoid material appeared. In these same areas the alveolar cells were more prominent and some distended capillaries were in the thickened septae. The pink-staining proteinoid material tended to fill most alveolar spaces but did not stream through or "bridge" the interalveolar pores. Multinucleated giant cells were seen rarely. Terminal bronchioles contained very little of the proteinoid material. Inflammatory reaction was minimal to absent except in the neighborhood of the abscess which had the appearance of being moderately old. Sclerosis of the pulmonary vessels was not noted. Mediastinal lymph nodes showed no evidence of the proteinoid material. Special stains revealed normal findings except the Masson trichrome stain which documented the interstitial fibrosis. Other stains

were Turnbull's blue, McManus periodic acid, Heidenhain's iron hematoxylin, Gram-Weigert, Sudan IV, Schultz, Mayer's mucicarmine and Dopa.

Other autopsy findings consisted of a shallow chronic peptic ulcer of the stomach, and some thinning of the adrenal cortex. The kidneys were normal grossly, but microscopically a fine scarring extended from the subcapsular area toward the pelvis. An occasional mildly dilated tubule, lined by atrophic or irregular epithelium and containing hyaline scars, was nearby. Renal vascular changes had not occurred. The heart weighed 325 Gm. and the thickness of the right and left ventricles was 2 and 16 mm., respectively. The liver and spleen were normal.

COMMENT

The longer this patient was observed, two clinical impressions assumed prominence. At first, berylliosis was considered a definite possibility, in view of his contact with fluorescent lights; however, since granulomas suggestive of berrylliosis were not seen at any time, the presence of this condition was thought unlikely. Secondly, Hamman-Rich syndrome was contemplated.

At the time of lung biopsy, the description of the gross appearance of the lung was compatible with the Hamman-Rich syndrome, but microscopic sections showed only slight fibrosis of the alveolar walls and the most outstanding finding was pink-staining material in the alveolar spaces. A diagnosis of Hamman-Rich syndrome could not be ruled out completely, however, as only one case of the syndrome in which lung biopsy had been done soon after onset of symptoms had been reported in the literature. This case was reported by Pinney and Harris,[2] and biopsy had been obtained within four months after the onset of symptoms and before treatment was begun. Since the *early* microscopic picture of the Hamman-Rich syndrome was essentially unknown, our case could have represented early findings. Subsequently, at least two other cases[3, 4] in which lung biopsy was done soon after onset of symptoms have been reported. These, together with Pinney's case, indicate that the fundamental microscopic and pathologic features of the Hamman-Rich syndrome are seen early and do not change markedly with the duration of symptoms.

In sections of the lungs at autopsy, the outstanding feature again was the pink-staining intra-alveolar material as seen in the biopsy. Numerous special staining techniques failed to identify its nature or origin. Interstitial fibrosis, while greater than in the biopsy specimen, was present only to a moderate degree and did not appear to be of the type originally described by Hamman and Rich. However, our patient received prolonged (eight months) corticosteroid and oxygen therapy, and these may have influenced the final microscopic picture in the lungs. Although it is doubtful that corticosteroid therapy alters the fundamental pathologic features of the Hamman-Rich syndrome, it is conceivable that this therapy could alter the tissue response in other conditions.

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Intrathoracic Neuroma of the Right Phrenic Nerve

Case Report

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Los Angeles, California

Up to now, the literature reveals a large number of instances of neurogenic tumors in the chest. For purposes of discussion, only a few are cited. These reports may be divided into three groups: (a) intrathoracic neurogenic tumors *per se;* (b) those found on the vagus nerve as a site; and (c) those revealing the source as the Schwann cell.

Intrathoracic Neurogenic Tumors Per Se

Malignancy: Kent, Blades, Valle and Graham[1] found that intrathoracic neurogenic tumors were malignant in 37 per cent and 41 per cent of a total of 19 and 105 patients respectively. Efskind and Liavaag[2] found that in 21 neurogenic tumors, those in the posterior mediastinum were usually benign whereas those in the anterior mediastinum were malignant.

Site: Neurogenic tumors are found most commonly in the posterior mediastinum and the posterior gutters. They are seen frequently at the intervertebral foramina, perhaps as a "collar button," in the intercostal spaces, and are covered by pleura, as Lavender and Prentice[3] and Harrington[4] point out. A neurilemmoma was found by the author attached to the fourth left intercostal nerve anteriorly.* Other than the spinal nerves and roots, neurogenic tumors have been found on the vagi, as reported by Tuttle and Harms,[5] Furrer and Fox,[6] Blades and Dugan,[7] Gilbertsen and Lillehei,[8] and Gerbode and Marguiles;[9] and the sympathetic chain, as reported by Blades and Dugan.[7]

*J. A. J. (Case No. 80323), operated upon at St. Francis Hospital, May 27, 1954.

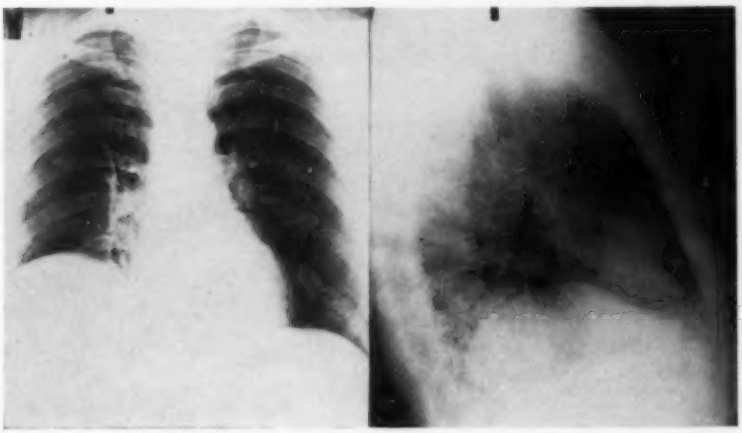

FIGURE 1 FIGURE 2

Figure 1: PA view of the chest, showing the elevated right diaphragm and questionable lesion in the medial lower region of the right lung.—*Figure 2:* Right lateral view, showing the elevated right diaphragm.

Schwann Cell as Origin

Murray and Stout[10] as well as Masson[11] have shown that the Schwann cell appears to be the source of this tumor; that is, the neurilemmoma. Their cultures have given adequate evidence.

Size

The size of these tumors may vary from 6 mm. (neuroma, as presented below) to 6 cm. and 12 cm. (in Cutler's series), the latter weighing 326 grams.[12]

The case presented herewith is for a twofold purpose: That it is the first neurogenic tumor reported found arising from the phrenic nerve; and that the pathologic diagnosis is a neuroma. There was no history of trauma.

FIGURE 3: Planogram at 9 cm., showing pooled dye and questionable lesion in the right lower lobe.

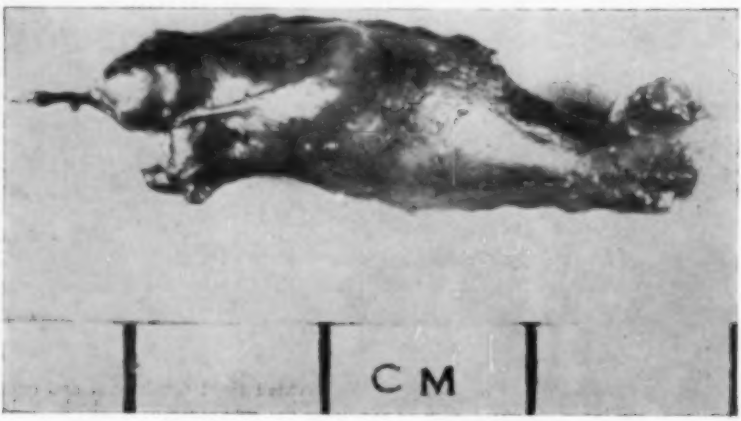

FIGURE 4: Photograph of specimen, showing actual size.

Case Report

J. V. (Case No. 1677), a 39-year old white man was first seen on February 4, 1954. He stated he had taken a trip three weeks previously, when he ingested some food which "did not set well in his stomach." He consulted his doctor for the stomach discomfort and gastrointestinal x-ray films were made. These were reported to be normal. A chest x-ray film, however, revealed a "lesion in the right lung," (Figs. 1 and 2) for which he was referred for consultation.

He complained mainly of a mild abdominal discomfort which in itself did not fit the usual ulcer pattern. There was no further positive history except that his sleep had been poor lately due to a slight anxiety about his illness. He denied any recent or old history of trauma or injury. Physical examination revealed a six-foot man weighing 217 pounds, with a temperature of 99° F., pulse 69 and blood pressure 120/80.

The positive findings were: A few rhonchi elicited at the right base of the chest; a high right hemidiaphragm as seen on fluoroscopy with paradoxic motion; and a questionable shadow in the area of the posterior segment of the right lower lobe.

The hemogram and urinalysis were normal.

Upon bronchoscopic examination, the right lower lobe bronchus appeared to be telescoped within itself, not unlike an intussusception, and this presented a false appearance of an intraluminal tissue mass. Nevertheless, a biopsy was taken and revealed no evidence of tumor. Bronchial washings disclosed no evidence of malignant cells. Bronchograms and planograms were done, the former revealing some pooling of the dye in the right lower lobe area. (It could not be said whether the lipiodol-filled bronchus was an irregularly shaped cavity or pooled dye.) (Fig. 3) The planograms at 9 and 10 cm. revealed a shadow which appeared to be associated intimately with the right main lower lobe bronchus. Although the radiologic reading favored a tumor mass, the author did not agree in reviewing the films.

The positive findings were, therefore, a paralyzed right hemidiaphragm; a questionable shadow in the right lower lobe area, which could be tumor or compressed lung; and a 99° temperature, which could arise from the compressed lung or atelectasis beyond a tumor. Thoracotomy was indicated, with a preoperative diagnosis of tumor involving the right phrenic nerve.

On February 12, 1954, he was admitted to the Queen of Angels Hospital. Right thoracotomy revealed a tumor nodule on the right phrenic nerve over the superior vena cava measuring 13x6x6 mm. (Fig. 4) It was resected successfully and he made an uneventful recovery.

The pathologic diagnosis was neuroma of the right phrenic nerve. The resected specimen measured 3.5 cm. in length. In the midportion, there was a distinct fusiform swelling on the nerve. Here, imbedded on the midportion of the nerve was an oval, encapsulated tumor-nodule measuring 13x6x6 mm. The cut surface was gray, moist and partly translucent.

Microscopic examination of a complete transverse section taken from the midportion of the specimen showed the tumor nodule to be composed of numerous closely grouped bundles of nerve fibers with very little supportive connective tissue stroma. The nerve fibers were swollen and showed degenerative changes. The nuclei were small and pyknotic. There was no pleomorphism. Around the periphery, there was a thin, fibrous, capsular formation outside of which there was a small amount of loose areolar connective tissue and also some fat.

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PROCEEDINGS OF THE ANNUAL MEETING

The Board of Regents and the Board of Governors of the College held their annual meetings in Atlantic City, in connection with the Silver Anniversary Meeting of the College, June 3-7, at the Ambassador Hotel. The following Regents, Governors, Chapter Delegates, council and committee chairmen, and guests were officially registered:

Regents

John F. Briggs, St. Paul, Minnesota, Chairman

Donato G. Alarcon, Mexico City, Mexico
Arnold S. Anderson, St. Petersburg, Florida
Albert H. Andrews, Chicago, Illinois
Carl C. Aven, Marietta, Georgia
Andrew L. Banyai, Chicago, Illinois
Otto L. Bettag, Chicago, Illinois
Dean B. Cole, Richmond, Virginia
Johann L. Ehrenhaft, Iowa City, Iowa
Seymour M. Farber, San Francisco, California
M. Jay Flipse, Miami, Florida
Samuel J. Forrest, Toronto, Ontario, Canada
Carl H. Gellenthien, Valmora, New Mexico
Alfred Goldman, St. Louis, Missouri
Burgess L. Gordon, Albuquerque, New Mexico
Edward A. Greco, Portland, Maine
Alvis E. Greer, Houston, Texas
Edward W. Hayes, Sr., Monrovia, California
George R. Herrmann, Galveston, Texas
William A. Hudson, Detroit, Michigan
Chevalier L. Jackson, Philadelphia, Pennsylvania
Hollis E. Johnson, Nashville, Tennessee
Donald R. McKay, Buffalo, New York
Herman J. Moersch, Rochester, Minnesota
Edward H. Morgan, Seattle, Washington
J. Arthur Myers, Minneapolis, Minnesota
Arthur M. Olsen, Rochester, Minnesota
J. Winthrop Peabody, Sr., Washington, D.C.
Charles K. Petter, Waukegan, Illinois
Joseph C. Placak, Sr., Abingdon, Virginia
Elmer C. Rigby, Los Angeles, California
James H. Stygall, Indianapolis, Indiana
Howard S. Van Ordstrand, Cleveland, Ohio
David H. Waterman, Knoxville, Tennessee
Irving Willner, Newark, New Jersey

Governors

Howell Randolph, Phoenix, Arizona, Chairman

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Robert J. Anderson, Atlanta, Georgia
Paul W. Auston, Langdale, Alabama
Albert Aranson, Portland, Maine
Gerald A. Beatty, Wilmington, Delaware
B. Guy Begin, Montreal, Quebec, Canada
Otto C. Brantigan, Baltimore, Maryland
Charles A. Brasher, Mt. Vernon, Missouri
Paul J. Breslich, Minot, North Dakota
A. Albert Carabelli, Trenton, New Jersey
Ross K. Childerhose, Harrisburg, Pennsylvania
Sumner S. Cohen, Oak Terrace, Minnesota
Winthrop N. Davey, Ann Arbor, Michigan
Edgar W. Davis, Washington, D.C.
Everett C. Drash, Charlottesville, Virginia
Max Fleishman, Omaha, Nebraska
William P. Gray, Batesville, Arkansas
Joseph E. J. Harris, Albuquerque, New Mexico
John S. Harter, Louisville, Kentucky
Henry R. Hoskins, San Antonio, Texas
Miguel Jimenez, Mexico City, Mexico
Francis J. Kasheta, Glencliff, New Hampshire
Ray W. Kissane, Columbus, Ohio
John A. Lewis, London, Ontario, Canada
Alexander Libow, Miami Beach, Florida
Ezequiel Martinez-Rivera, Hato Rey, Puerto Rico
George R. Maxwell, Morgantown, West Virginia
Donald W. McCauley, Okmulgee, Oklahoma
Angus R. McPherson, Saskatoon, Sask., Canada
Francisco J. Menendez, Havana, Cuba
Frank A. Merlino, Providence, Rhode Island
Ralph E. Moyer, Oteen, North Carolina
Jerome V. Pace, Rockville, Indiana
Charles Pokorny, Halstead, Kansas
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William R. Rumel, Salt Lake City, Utah
J. Gordon Seastrunk, Columbia, South Carolina
Lloyd M. Taylor, Great Falls, Montana
Mauricio Teichholz, Rio de Janeiro, Brazil
Carl W. Tempel, Washington, D.C.
Peter A. Theodos, Philadelphia, Pennsylvania
Darrell H. Trumpe, Springfield, Illinois
Kenneth A. Tyler, Gooding, Idaho
Jose Francisco Valiente, San Salvador, El Salvador
Buford H. Wardrip, San Jose, California
Roy A. Wolford, Washington, D.C.
W. Bernard Yegge, Denver, Colorado

Chapter Delegates

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Rogelio J. Barata, Havana, Cuba
Lewis F. Baum, South Orange, New Jersey
George S. Bond, Indianapolis, Indiana
Howard A. Buechner, New Orleans, Louisiana
Charles P. Cake, Arlington, Virginia
Arthur A. Calix, Decatur, Alabama
Fred B. Champlin, Milwaukee, Wisconsin
Alberto Chattas, Cordoba, Argentina
James T. Cheng, Pontiac, Michigan
David A. Cooper, Philadelphia, Pennsylvania
DeWitt Daughtry, Miami, Florida
Alfred D. Dennison, Jr., Indianapolis, Indiana
John L. Elliott, Savannah, Georgia
John B. Floyd, Jr., Lexington, Kentucky
Millard Jeffrey, Phoenix, Arizona
David E. Garcia, Hato Rey, Puerto Rico
Arthur C. Knight, Deer Lodge, Montana
Francis G. Kravec, Youngstown, Ohio
Andre Mackay, Montreal, Quebec, Canada
Leopoldo Molinari, Lima, Peru
Robert B. Morrison, Austin, Texas
William Nice, Topeka, Kansas
Morris H. O'Dell, Charleston, West Virginia
Maurice S. Segal, Boston, Massachusetts
Robert M. Shepard, Jr., Tulsa, Oklahoma

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Charles P. Bailey, Philadelphia, Pennsylvania
Alfredo Cesanelli, Rosario, Argentina
Eliot Corday, Beverly Hills, California
Stephen Elek, Los Angeles, California
Benjamin M. Gasul, Chicago, Illinois
Roy F. Goddard, Albuquerque, New Mexico
Harry Goldberg, Philadelphia, Pennsylvania
John S. LaDue, New York, New York
William M. Lees, Chicago, Illinois
Henry W. Leetch, Saranac Lake, New York
William Likoff, Philadelphia, Pennsylvania
Arthur M. Master, New York, New York
H. Easton McMahon, New York, New York
Milton Mendlowitz, New York, New York
Arnold Minnig, Denver, Colorado
H. Allan Novack, Boston, Massachusetts
Antonio Rodrigues Diaz, Havana Cuba
Israel Steinberg, New York, New York
William C. Voorsanger, San Francisco, California

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Murray Kornfeld, Chicago, Illinois, Executive Director
Ward Bentley, Chicago, Illinois, Executive Assistant
Harriet L. Kruse, Chicago, Illinois, Executive Assistant
Margaret Rogers, Chicago, Illinois, Executive Assistant

Joint Meeting of the Board of Governors and the Board of Regents

The annual joint meeting of the Governors and Regents was held during lunch on Thursday, June 4. Dr. Howell S. Randolph, Chairman of the Board of Governors, presided at the meeting. Certificates of Merit were awarded to the following Past Presidents of College Chapters by Dr. Donald R. McKay, President:

James L. Alexander, Georgia Chapter
James O. Armstrong, Texas Chapter
Lewis F. Baum, New Jersey Chapter
Edmund G. Beacham, Potomac Chapter
George S. Bond, Indiana Chapter
Arthur A. Calix, Alabama Chapter
Stephen M. Gelenger, Michigan Chapter
Carl H. Gellenthien, New Mexico Chapter
Thomas N. Hunnicutt, Jr., Virginia Chapter
Wilbur F. Jehl, New Jersey Chapter
Roy G. Klepser, Potomac Chapter
Ross C. Kory, Wisconsin Chapter
J. Paul Medelman, Minnesota Chapter
Frank W. Pickell, Louisiana Chapter
Elmer C. Rigby, California Chapter
Robert M. Shepard, Jr., Oklahoma Chapter

Reports were received from the following councils, committees and sections:

Committee on Undergraduate Medical Education
William M. Lees, Chicago, Illinois, Chairman

Committee on College Essay Contest
H. Allan Novack, Boston, Massachusetts, Chairman

Council on Postgraduate Medical Education
J. Winthrop Peabody, Sr., Washington, D.C., Chairman

College Books
Burgess, L. Gordon, Albuquerque, New Mexico

Council on Research
Arthur M. Olsen, Rochester, Minnesota, Vice-Chairman

Committee on Non-Surgical and Drug Therapy
Alexander Libow, Miami Beach, Florida, Chairman

Committee on Inhalation Therapy
Albert H. Andrews, Chicago, Illinois, Chairman

Sections on Cardiovascular Disease:

Section on Clinical Cardiovascular Disease
Eliot Corday, Beverly Hills, California, Chairman

Section on Cardiovascular Surgery
Charles P. Bailey, Philadelphia, Pennsylvania, Chairman

Section on Pediatric Cardiology
Benjamin M. Gasul, Chicago, Illinois, Chairman

Section on Electrocardiography
Stephen R. Elek, Los Angeles, California, Chairman

Section on Rehabilitation
H. Easton McMahon, New York City, Chairman

Section on Cardiovascular Physiology
John S. LaDue, New York City, Secretary

Section on Angiocardiography and Roentgenology
Israel Steinberg, New York City, Chairman

Committee on Cardiovascular Disease
Arthur M. Master, New York City, Chairman

Council on Hospitals and Joint Committee on Chest X-Ray
Otto L. Bettag, Chicago, Illinois, Chairman

Committee on Membership
Chevalier L. Jackson, Philadelphia, Pennsylvania, Chairman

Council on International Affairs
Andrew L. Banyai, Chicago, Illinois, Chairman

Silver Anniversary, Homecoming Meeting
Roy F. Goddard, Albuquerque, New Mexico

Silver Anniversary, Interim Session
Alvis E. Greer, Houston, Texas

Messages were read from General S. U. Marietta, Washington, D.C., and Dr. Richard H. Overholt, Boston, Massachusetts, past-presidents of the American College of Chest Physicians, who expressed regrets for their inability to be present for the Silver Anniversary Meeting of the College, and extending their best wishes for a successful session.

Dr. George R. Maxwell, Morgantown, West Virginia, was elected by the Board of Governors to the Committee on Nominations.

Dr. Howell S. Randolph, Phoenix, Arizona, was re-elected Chairman of the Board of Governors.

Annual Meeting, Board of Regents

The Board of Regents of the College held its annual meeting on Wednesday afternoon, June 3, at the Ambassador Hotel, Atlantic City, and a second meeting of the Board was held on Sunday, June 7. Dr. John F. Briggs, Chairman of the Board of Regents, presided.

Dr. Charles K. Petter presented the report of the Treasurer and the report of the Committee on Insurance, which were unanimously approved. The Report of the Treasurer was published in the July issue of *Diseases of the Chest*.

Dr. Andrew L. Banyai presented the report of the Reference Committee on the Report of the Committee on Microbiology. It was recommended and approved that the report be published in full as soon as possible. This report will appear in an early issue of *Diseases of the Chest*.

Dr. Albert H. Andrews presented the report of the Council on Research wherein it was recommended that the council be divided into two sections, one on cardiovascular diseases and one on pulmonary diseases, with co-chairmen for each section and one overall chairman. The Board of Regents unanimously approved this proposal and recommended that the reorganization of the Council on Research be established pro-tem until the necessary amendment in the College bylaws is made by the Committee on Bylaws and officially voted on by the membership.

Dr. Andrews presented resumés of the reports of the committees and sections serving under the Council on Research. These reports will be published in subsequent issues of the College journal, *Diseases of the Chest*.

Dr. Carl H. Gellenthien, Chairman of the Committee on Indian Affairs of the College, introduced Dr. Julius L. Wilson, Director of the Henry Phipps Institute, University of Pennsylvania, in charge of the New Mexico Indian Tuberculosis Prevention Study, sponsored by the College committee, under the authorization of the U. S. Public Health Service. Dr. Wilson reported on the progress of the study and announced that a complete report would be available for publication in *Diseases of the Chest* in the near future. The Board of Regents expressed its appreciation to Dr. Wilson for his report and pledged its continued support.

Dr. David B. Radner, Chairman of the Board of Examiners, reported that 36 candidates for Fellowship in the College had taken oral and written examinations in Atlantic City on June 4, as compared to 21 last year. The multiple-choice questions had been continued, which the Board of Examiners felt was most acceptable.

The appointment of a Vice-Chairman of the Board of Regents was discussed and it was unanimously agreed that one be elected pro-tem, pending the study of this matter by the Committee on Bylaws.

The report of the Editorial Board, submitted by Dr. J. Arthur Myers, Editor-in-Chief, was presented and unanimously approved. Dr. Seymour M. Farber, newly elected President of the College, announced the appointment of the following chairmen for the 26th Annual Meeting of the College to be held in Miami Beach, Florida, June 8-12, 1960:

Dr. Thomas M. Mattingly, Washington, D.C.
Section on Cardiovascular Diseases

Dr. R. Drew Miller, Rochester, Minnesota
Section on Pulmonary Diseases

The following officers were elected:

Dr. Burgess L. Gordon, Albuquerque, New Mexico, to the Committee on Nominations

Dr. Alfred Goldman, St. Louis, Missouri, re-elected a member of the Executive Council

Dr. Henry C. Sweany, Mt. Vernon, Missouri, re-elected a member of the Editorial Board for *Diseases of the Chest*

Dr. Arthur M. Olsen, Rochester, Minnesota, Chairman of the Board of Regents
Dr. Irving Willner, Newark, New Jersey, Vice-Chairman of the Board of Regents

The following resolutions were read and approved:

WHEREAS, Since the time of its foundation the American College of Chest Physicians has achieved fabulous growth, world-wide recognition and unblemished prestige, and

WHEREAS, The American College of Chest Physicians has accomplished through its manifold activities outstanding contributions to the progress of science, medical education and the welfare of mankind, and

WHEREAS, All these attainments would not have been possible without methodical organization, prudent foresight and indefatigable endeavors, and

WHEREAS, The faithful, dedicated, devoted and unrelenting service of Mr. Murray Kornfeld, Executive Director of the College, combined with diplomacy and adroitness, has guided the success of this organization in such an extraordinary manner during the past 25 years,

THEREFORE BE IT RESOLVED, That the Board of Regents request Mr. Murray Kornfeld to continue his excellent services as Executive Director of the College as heretofore.

The Board of Regents of the American College of Chest Physicians expresses its approval of the educational programs fostered by the various state chapters of the College. The Board wishes to encourage the chapters to support postgraduate medical education within their states. However, it is desirable that the teaching activities of the individual chapters be correlated with the educational programs offered by other chapters and the national organization. The Council on Postgraduate Medical Education should offer help and advice to the state chapters in matters concerning finance as well as scientific program. By channeling all teaching activities through the Council, a well-rounded postgraduate educational program should be achieved.

THEREFORE BE IT RESOLVED, That all Chapters of the College desirous of participating in postgraduate medical education submit to the Council on Postgraduate Medical Education their proposed postgraduate courses for the consideration and approval of the Council on Postgraduate Medical Education.

WHEREAS, The American College of Chest Physicians is of the opinion that the physician in the general practice of medicine holds a key position in the fight against tuberculosis, and

WHEREAS, The College since its inception has in many ways attempted to keep the physician in the general practice of medicine apprised of the most recent developments in the field of tuberculosis and other chest conditions, and

WHEREAS, The College has for a number of years encouraged the organization of tuberculosis committees in the State and County Medical Societies, and

WHEREAS, These committees can and should serve a useful purpose in bringing to the attention of the physician in the general practice of medicine the most recent information concerning the diagnosis and treatment of tuberculosis,

THEREFORE, BE IT RESOLVED, That the Committee on Tuberculosis of the American College of Chest Physicians continue to exert its influence to urge every State and County Medical Society in the United States to have a tuberculosis committee and that these committees cooperate with the State and County Tuberculosis Societies within their respective areas so that together they may bring to the attention of the physician in the general practice of medicine such information which will eventually result in the eradication of tuberculosis, and

BE IT FURTHER RESOLVED, That the public should be encouraged to continue their purchase of Christmas Seals because tuberculosis is still the number one killer of all infectious diseases.

WHEREAS, The Hospital Counselor, a publication sponsored by the Council on Hospitals of the College, has been most successful and well received since its inception in April, 1953, and

WHEREAS, It is anticipated that the regular publication of the brochure will be continued, BE IT RESOLVED that the name be changed to The Public Health Counselor in order to broaden the field of articles which might be included in this publication to all phases of chest disease, including cancer, cardiology, tuberculosis, etc. and

BE IT FURTHER RESOLVED, That this publication be sponsored jointly by the Council on Hospitals and the Council on Public Health of the American College of Chest Physicians.

WHEREAS, The Territory of Alaska has become the 49th State of the Union and is geographically in the area which comprises regional district No. 14, and

WHEREAS, The State of Utah, upon the request of College members in that state, is now included in district No. 14, comprising the Pacific Northwest Chapter,

BE IT RESOLVED, That the State of Alaska be included in regional district No. 14 and that the State of Utah be transferred from regional district No. 11 to district No. 14 so that it may be included in the Pacific Northwest States, and

BE IT FURTHER RESOLVED, That the State of Arizona be transferred from regional district No. 13 to district No. 11 which comprises the states of New Mexico, Colorado and Wyoming.

NEWS NOTES

Dr. William E. Adams

During the College Convocation in Atlantic City, June 4, Honorary Membership in the Brazilian Tuberculosis Society was conferred upon **Dr. Donald R. McKay,** Buffalo, New York, outgoing President of the College, and **Dr. Seymour M. Farber,** San Francisco, California, incoming President. **Dr. Mauricio Teichholz,** Governor of the College for Rio de Janeiro, presented Drs. McKay and Farber with their membership certificates and also presented the Brazilian flag to the College in behalf of the nine College chapters in his country.

Dr. William E. Adams, Chicago, was elected President of the American Association for Thoracic Surgery at its annual meeting held in Los Angeles, April 21-23. Dr. Adams, who has served as chairman of the Illinois Committee on Membership for several years, is, at the present time, President-Elect of the Illinois Chapter of the College and is Vice-Chairman of the national Committee on Pulmonary Surgery.

CHAPTER NEWS

Italian Chapters

The Italian Chapters of the College held their Fifth Scientific Session at the Carlo Forlanini Institute in Rome, May 17. The meeting attracted a large attendance and an excellent program covering clinical and surgical aspects of pulmonary and cardiovascular disease was presented by members of the College representing all sections of Italy and the leading medical schools. Prof. Dr. A. Omodei Zorini, Director of the Carlo Forlanini Institute and Regent of the College for Italy, welcomed the members and guests and introduced Prof. Dr. Eugenio Morelli of Rome, Honorary Regent, who presided at the scientific session. The papers presented at this meeting will be published in the Italian "Review of Tuberculosis and Diseases of the Respiratory System" and in the "Annals of the Carlo Forlanini Institute."

Kentucky Chapter

The annual meeting of the Kentucky Chapter will be held in Louisville, September 23, in conjunction with the state medical association meeting. Dr. Herbert Sloan, Ann Arbor, Michigan, will speak on "Congenital Heart Disease."

Virginia Chapter

The Virginia Chapter will hold its annual meeting in Roanoke on Sunday, October 4, at the Hotel Roanoke. The following program will be presented, starting at 2:00 p.m.:

"Diseases of the Esophagus"
W. C. Sealy, Durham, North Carolina
"Evaluation of Pulmonary Function"
John L. Guerrant, Charlottesville, Virginia
Presentation: Three Cases, "Pulmonary Disease Presumably Due to Atypical Acid-fast Bacilli"
L. R. Broome, Catawba, Virginia

ANNOUNCEMENT

The Department of Otolaryngology, University of Illinois College of Medicine, announces the following two special postgraduate courses to be offered in the fall:

Annual Otolaryngologic Assembly, September 18-26.

Course in Laryngology and Bronchoesophagology, November 9-21.

Chairmen of the otolaryngology course are Drs. Maurice F. Snitman and Emanuel M. Skolnik, and Dr. Paul H. Holinger is chairman of the course on laryngology and bronchoesophagology. Interested physicians should write directly to the Department of Otolaryngology, 1853 West Polk Street, Chicago 12, Illinois.

HOMECOMING MEETING

SILVER ANNIVERSARY, AMERICAN COLLEGE OF CHEST PHYSICIANS

Albuquerque, New Mexico

October 14-17, 1959

Headquarters: Western Skies Hotel

PROGRAM

Wednesday, October 14

10:00 a.m.—Registration, East Lobby

The Registration Desk will be open from 10:00 a.m. to 5:00 p.m. at the Western Skies Hotel. All physicians are cordially invited to attend; there is no registration fee.

Technical Exhibits, Manzano and Tijeras Rooms

The Technical Exhibits will open at 10:00 a.m., Wednesday, October 14, and will be open from 8:30 a.m. to 2:30 p.m. through Saturday, October 17.

8:00 p.m.—Opening Session, Sandia Room

Chairmen:

Seymour M. Farber, San Francisco, California
President, American College of Chest Physicians
M. Jay Flipse, Miami, Florida
President-Elect, American College of Chest Physicians

Introductions:

Mr. Maurice Sanchez, Commissioner, City of Albuquerque, New Mexico
Hon. John Burroughs, Governor, State of New Mexico
Lewis M. Overton, President, New Mexico State Medical Society

Address:

"The First Round-up"
J. Arthur Myers, Minneapolis, Minnesota
"The Clinical Examinations of Space Candidates"
W. Randolph Lovelace II, Albuquerque, New Mexico

Entertainment, Patio

Thursday, October 15

8:55 a.m.—Scientific Session No. 1, La Mina Room

REPORTS SUMMARIZING TECHNICS AND THEIR APPLICATIONS IN THE STUDY AND TREATMENT OF HEART DISEASE

Chairman:

Merril Brown, Albuquerque, New Mexico

9:00 a.m.—The Double Catheter Technic for Determining Intracardiac Shunts
Albert L. Hyman, New Orleans, Louisiana

9:10 a.m.—The Timing of Spatial Vectorcardiogram in Diagnosis
Lewis Gunther, Los Angeles, California

9:20 a.m.—A Simplification of Various Vectorcardiographic Lead Systems
Stephen R. Elek, Los Angeles, California

9:30 a.m.—Abdominal Aortoarteriography
André J. Bruwer, Tucson, Arizona

9:40 a.m.—Further Experience with a Simple Method for Recognition and Quantitation of Aortic Stenosis
JD Mortenson, Alan F. Toronto and Homer R. Warner, Salt Lake City, Utah

9:50 a.m.—Clinical Use of the Pump-Oxygenator Without Blood for Prime or Support During Perfusion
Wilford B. Neptune, Boston, Massachusetts

10:00 a.m.—The Selection of a Cardiopulmonary Bypass System
Ralph Berg, Henry Lang and Richard Kleaveland, Spokane, Washington

10:10 a.m.—Prolonged Veno-Arterial Pumping for Circulatory Support
James W. Dow, James F. Dickson III, and Neil A. J. Hamer, Philadelphia, Pennsylvania

Thursday, October 15, Continued

10:20 a.m.—*The Immediate Hemodynamic Effects of Mitral Commissurotomy*
Elliot Rapaport, San Francisco, California

10:30 a.m.—*The Application of Perioral Endoscopy in Cardiovascular Disease*
Walter H. Maloney, Cleveland, Ohio

10:40 a.m.—*An Original Surgical Technic for the Treatment of Aortic Valvular Disease*
Alfred Goldman, Beverly Hills, California

10:55 a.m.—*Mitral Insufficiency; Its Surgical Correction by Open Technic*
Dwight E. Harken and Warren J. Taylor, Boston, Massachusetts

11:10 a.m.—*Adjournment*

8:55 a.m.—*Scientific Session No. 2, Sandia Room*

PERTINENT ASPECTS IN THE STUDY AND TREATMENT OF PULMONARY DISEASE: ANATOMY, PATHOLOGY AND PHYSIOLOGY

Chairman:
H. Crawford Jernigan, Fort Stanton, New Mexico

9:00 a.m.—*Comparative Anatomy of the Lungs in Mammals, Including Man, and Its Possible Clinical Significance*
Lt. Richard F. McLaughlin Jr., MC, USN, and Gerald L. Crenshaw, Oakland, California; Capt. Robert O. Canada, MC, USN, Bethesda, Maryland; and Walter S. Tyler, D.V.M., Ph.D., Davis, California

9:15 a.m.—*Pathology of the Lung: Recent advances*
William E. Hentel and A. N. Longfield, Albuquerque, New Mexico

9:30 a.m.—*Ischemic Necrosis in Anthracosilicosis: An Illustrative Problem in Chronic Pulmonary Disease*
Peter A. Theodos, Philadelphia, Pennsylvania

9:45 a.m.—*The Structural Basis for Pulmonary Dysfunction*
Howard G. Dayman, Buffalo, New York

10:00 a.m.—*Interrelationship of Ventilation and the Pulmonary Circulation*
John Rankin, Madison, Wisconsin

10:15 a.m.—*Studies on Air Distribution in Pulmonary Emphysema*
Hurley L. Motley, Los Angeles, California

10:30 a.m.—*The Rationale of Physiologic Therapy in Chronic Pulmonary Disease*
Reginald H. Smart, Los Angeles, California

10:45 a.m.—*RECESS TO VISIT EXHIBITS*

11:00 a.m.—*BELOW THE SEA—UP IN THE AIR*

Chairman:
J. E. J. Harris, Albuquerque, New Mexico

11:05 a.m.—*Skin Diving: Hazards and Preventive Measures*
Capt. Gerald J. Duffner, MC, USN, Washington, D.C.

11:25 a.m.—*Human Body Density and Its Significance in Clinical Medicine*
Thomas P. K. Lim, Albuquerque, New Mexico

11:45 a.m.—*Acclimatization to High Altitude*
Ulrich C. Luft, Albuquerque, New Mexico

12:05 p.m.—*Adjournment*

12:30 p.m.—ROUND TABLE LUNCHEON MEETINGS

A-1 *Mechanics of Breathing, with Special Reference to Medical and Surgical Problems*
Joseph Gordon, Albuquerque, New Mexico, *Moderator*
Ross C. Kory, Milwaukee, Wisconsin
William F. Miller, Dallas, Texas
Ralph G. Rigby, Salt Lake City, Utah
Joseph F. Tomashefski, Columbus, Ohio

A-2 *Acquired Valvular Heart Disease*
Milton W. Anderson, Rochester, Minnesota, *Moderator*
Charles P. Bailey, Philadelphia, Pennsylvania
André J. Bruwer, Tucson, Arizona
Thomas N. James, Detroit, Michigan

A-3 *Diuretics*
Stewart Wolf, Oklahoma City, Oklahoma, *Moderator*
Robert Friedenberg, Albuquerque, New Mexico
Thomas W. Mattingly, Washington, D.C.
John H. Moyer, Philadelphia, Pennsylvania

Friday, October 16

8:55 a.m.—Scientific Session No. 3, La Mina Room

UNRELATED PAPERS ON SPECIAL PROBLEMS OF THE HEART, LUNGS AND MEDIASTINUM

Chairman:

Charles K. Petter, Waukegan, Illinois

9:00 a.m.—*The Diagnosis and Treatment of Thyoma*
John L. Pool, New York, New York

9:15 a.m.—*The Role of Esophageal Motility Studies in Evaluating Thoracic Pain*
Howard A. Andersen, Rochester, Minnesota

9:30 a.m.—*Unusual Types of Esophageal Obstruction*
John N. Briggs, Los Angeles, California

9:45 a.m.—*Blast Injury of the Esophagus*
Howell S. Randolph, Phoenix, Arizona

10:00 a.m.—*Alterations of Pulmonary Function in Kyphoscoliosis and the Effects of Orthopedic Treatment*
Colin G. Caro, Thomas Glucker, Roy I. Peck and Arthur DuBois, Philadelphia, Pennsylvania

10:10 a.m.—*Pulmonary Complications and Treatment of Fibrocystic Disease of the Pancreas*
Henry J. Stanford, Tucson, Arizona

10:20 a.m.—*Three and A Half Years' Experience in the Treatment of Respiratory Insufficiencies, Including Emphysema, by Tracheal Fenestration*
E. E. Rockey, S. A. Thompson, and C. F. Blazsik, New York, New York

10:30 a.m.—*Ivalon Sponge Prosthesis with Pulmonary Resections; Over Five Years' Experience*
James E. Dailey, Houston, Texas

10:40 a.m.—*The Spectrum of Miliary Disorders of the Lungs*
Howard A. Buechner, New Orleans, Louisiana

10:50 a.m.—*Combined Mitral and Aortic Stenosis: Clinical and Hemodynamic Findings and Results of Surgery*
Joseph F. Uricchio, Philadelphia, Pennsylvania

11:00 a.m.—*The Manifestations of Disturbed Esophageal Function Mimicking Heart Disease*
Arthur M. Olsen, Rochester, Minnesota

11:10 a.m.—*Adjournment*

8:55 a.m.—Scientific Session No. 4, Sandia Room

MEDICINE AND SURGERY: RESPONSIBILITIES FOR THE CONTROL OF CARDIOPULMONARY DISEASE

Chairman:

Rodger E. MacQuigg, Albuquerque, New Mexico

9:00 a.m.—*Epidemiologic and Clinical Aspects of Sarcoidosis*
Martin M. Cummings, Washington, D.C.

9:15 a.m.—*Allergic States Associated with Chronic Pulmonary Disease*
William B. Steen, Tucson, Arizona

9:30 a.m.—*Differential Diagnosis Between Primary and Reinfection Types of Pulmonary Lesions*
J. Arthur Myers, Minneapolis, Minnesota

9:45 a.m.—*The Role of Ligation and Division of the Bronchus in the Surgical Treatment of Pulmonary Tuberculosis*
J. Maxwell Chamberlain, New York, New York

10:00 a.m.—*Chronic Cor Pulmonale*
Irving Mack, Chicago, Illinois

10:15 a.m.—*The Management of Pulmonary Heart Disease*
Maurice S. Segal, Boston, Massachusetts

10:30 a.m.—*Blast Biology: Pathology and Clinical Implications*
Clayton S. White, Albuquerque, New Mexico

10:45 a.m.—*RECESS TO VISIT EXHIBITS*

11:00 a.m.—*SYMPOSIUM ON ATHEROSCLEROSIS*

Chairman:

James K. Conrad, Albuquerque, New Mexico

11:05 a.m.—*Pathology of Atherosclerosis*
Thomas L. Chiffelle, Albuquerque, New Mexico

Friday, October 16, Continued

11:15 a.m.—Biochemical Features in Atherosclerosis
Bernard B. Longwell, Ph.D., Albuquerque, New Mexico

11:30 a.m.—The Most Recent Advances in Our Knowledge of Disturbed Carbohydrate Metabolism as a Possible Factor in Atherosclerosis
Howard F. Root, Boston, Massachusetts

11:45 a.m.—The Most Recent Conclusions on Cholesterol Metabolism in Atherosclerosis
Charles F. Wilkinson, Jr., New York, New York

12:05 p.m.—Adjournment

12:30 p.m.—ROUND TABLE LUNCHEON MEETINGS

B-1 Inhalation Therapy
Hurley L. Motley, Los Angeles, California, *Moderator*
Milton V. Davis, Dallas, Texas
Allan Hurst, Denver, Colorado
Roger H. L. Wilson, San Francisco, California

B-2 Atherosclerosis: Control Measures Through Dietetic Management
Herman J. Moersch, Rochester, Minnesota, *Moderator*
Robert U. Massey, Albuquerque, New Mexico
Howard F. Root, Boston, Massachusetts
Charles F. Wilkinson, Jr., New York, New York

B-3 Space Medicine: Medical and Engineering Preparations
W. Randolph Lovelace II, Albuquerque, New Mexico, *Moderator*
Ulrich C. Luft, Albuquerque, New Mexico
Albert H. Schwichtenberg, Albuquerque, New Mexico

3:30-5:00 p.m. "FIRESIDE CONFERENCES"

Subjects and Discussion Leaders

1. The Effects of Climatic Conditions on Pulmonary Diseases: Air Pollution, Humidity, Elevation
Albert H. Andrews, Chicago, Illinois
F. M. Murray, Durango, Colorado
Joseph F. Tomashefski, Columbus, Ohio
Hugh B. Woodward, II, Albuquerque, New Mexico

2. Coccidioidomycosis, Histoplasmosis and Mycoses: Prevention, Diagnosis and Treatment
Edward O. Egbert, El Paso, Texas
Orin J. Farness, Tucson, Arizona
Michael L. Furcolow, Kansas City, Kansas
Alvis E. Greer, Houston, Texas
James Kieran, Oakland, California
Solomon Netzer, Tucson, Arizona
Lloyd K. Swasey, Phoenix, Arizona

3. Management of Pulmonary Emphysema
George L. Baum, Coral Gables, Florida
Wesley A. Childs, Albuquerque, New Mexico
A. N. Longfield, Albuquerque, New Mexico
Hurley L. Motley, Los Angeles, California
T. E. A. von Dedenroth, Tucson, Arizona

4. Evaluation of the Cardiovascular System
Milton W. Anderson, Rochester, Minnesota
Charles R. Beeson, Albuquerque, New Mexico
Burton M. Cohen, Elizabeth, New Jersey
James W. Dow, Philadelphia, Pennsylvania
Stephen R. Elek, Los Angeles, California
Lewis Gunther, Los Angeles, California
Irving Mack, Chicago, Illinois

5. Coronary Disease: Medical and Surgical Aspects
Charles P. Bailey, Philadelphia, Pennsylvania
Albert L. Maisel, Albuquerque, New Mexico
JD Mortenson, Salt Lake City, Utah
Elliot Rapaport, San Francisco, California
Victor P. Satinsky, Beverly Hills, California

Fireside Conferences, Continued

6. *Inhalation Therapy: Apparatus and Technics*

Milton V. Davis, Dallas, Texas
Roy F. Goddard, Albuquerque, New Mexico
Allan Hurst, Denver, Colorado
Ross C. Kory, Milwaukee, Wisconsin
Edwin R. Levine, Chicago, Illinois
William F. Miller, Dallas, Texas
Maurice S. Segal, Boston, Massachusetts

7. *Mediastinal Disease*

Howard A. Buechner, New Orleans, Louisiana
A. Albert Carabelli, Trenton, New Jersey
Elmer C. Rigby, Los Angeles, California
Ralph G. Rigby, Salt Lake City, Utah
Robert Secrest, Albuquerque, New Mexico
Marcus Smith, Santa Fe, New Mexico

8. *Immunization in Tuberculosis*

Orville E. Egbert, El Paso, Texas
H. Crawford Jernigan, Fort Stanton, New Mexico
A. A. Leonidoff, Poughkeepsie, New York
E. Mary Mostyn, Albuquerque, New Mexico
J. Arthur Myers, Minneapolis, Minnesota

9. *Steroid Therapy in Heart and Lung Diseases*

John Abrums, Albuquerque, New Mexico
Edwin J. Grace, Brooklyn, New York
Morris Kaplan, Chicago, Illinois
Jacob J. Kirshner, Philadelphia, Pennsylvania
Donald B. Stewart, Albuquerque, New Mexico

10. *Asthma, Allergy*

M. L. Beach, Albuquerque, New Mexico
Clifford H. Kalb, Milwaukee, Wisconsin
Theodore Kircher, Albuquerque, New Mexico
Howard C. Leopold, Philadelphia, Pennsylvania
Edward Matzger, San Francisco, California
William B. Steen, Tucson, Arizona
Ralph L. Tingey, Salt Lake City, Utah
Leon Unger, Chicago, Illinois

11. *Medical-Surgical Chest Emergencies*

Merril Brown, Albuquerque, New Mexico
J. Ivan Hershey, Shreveport, Louisiana
Thomas F. Keyes, Las Vegas, Nevada
Rodger E. MacQuigg, Albuquerque, New Mexico
Howell Randolph, Phoenix, Arizona
Joseph F. Uricchio, Philadelphia, Pennsylvania
John R. Williams, Jacksonville, Florida

12. *Tuberculosis in Children*

Stuart Adler, Albuquerque, New Mexico
N. H. De Janney, Detroit, Michigan
Israel G. Epstein, Brooklyn, New York
Lester Karotkin, Houston, Texas
Estella Ford Warner, Albuquerque, New Mexico

13. *Surgical Procedures in Tuberculosis*

John N. Briggs, Los Angeles, California
J. Maxwell Chamberlain, New York City
Gerald L. Crenshaw, Oakland, California
Edward Dunner, Washington, D.C.
David Reisner, New York, New York
William F. Rienhoff, Jr., Baltimore, Maryland
Henry J. Stanford, Tucson, Arizona

14. *Industrial Pulmonary Diseases*

Harold L. Freedman, Albuquerque, New Mexico
William E. Hentel, Albuquerque, New Mexico
Edward Lebovitz, Pittsburgh, Pennsylvania
Israel Rappaport, New York, New York
Reuben I. Shapiro, Detroit, Michigan
Reginald H. Smart, Los Angeles, California
Peter A. Theodos, Philadelphia, Pennsylvania

Fireside Conferences, Continued

15. Technical Equipment for Thoracic Surgery: Research and Clinical
Ralph Berg, Jr., Spokane, Washington
Robert S. Cartwright, Albuquerque, New Mexico
James F. Dickson, III, Philadelphia, Pennsylvania
Alfred Goldman, Beverly Hills, California
Wilford B. Neptune, Boston, Massachusetts

16. Trace Metals in Myocardial Infarction
John H. Moyer, Philadelphia, Pennsylvania
Felix Wroblewski, New York, New York

17. Pulmonary Function Testing
David P. Cardus, Albuquerque, New Mexico
Richard T. Cathcart, Philadelphia, Pennsylvania
Thomas P. K. Lim, Albuquerque, New Mexico

18. Practical Clinical Problems in the Management of Congestive Failure
Albert N. Brest, Philadelphia, Pennsylvania
John F. Briggs, St. Paul, Minnesota
Albert L. Hyman, New Orleans, Louisiana
George Simson, Albuquerque, New Mexico

19. Special Technics in Radiologic Diagnosis
Colin G. Caro, Philadelphia, Pennsylvania
Omar Legant, Albuquerque, New Mexico

20. Newer Concepts in the Recognition and Treatment of Arrhythmias
William S. Blakemore, Philadelphia, Pennsylvania
James K. Conrad, Albuquerque, New Mexico

21. Treatment of Cor Pulmonale
Fred H. Hanold, Albuquerque, New Mexico
Louis A. Soloff, Philadelphia, Pennsylvania

22. Diet: Atherosclerosis and Coronary Heart Disease
Robert U. Massey, Albuquerque, New Mexico
Howard F. Root, Boston, Massachusetts

Saturday, October 17

8:55 a.m.—Scientific Session No. 5, La Mina Room

UNRELATED PAPERS ON THE MEDICAL STUDY AND TREATMENT OF CARDIAC AND PULMONARY DISEASE

Chairman:
Carl H. Gellenthien, Valmora, New Mexico

9:00 a.m.—*Massive Pulmonary Atelectasis in Ambulatory Patients with Voluntary Suppression of Cough*
Marvin S. Harris, Los Angeles, California

9:15 a.m.—*A Review of the Radiographic Changes Incident to Nonpenetrating Thoracic Trauma*
Lt. John R. Williams, MC, USN, Jacksonville, Florida

9:30 a.m.—*Applied Physiology in the Control of Cough*
Andrew L. Banyai, Chicago, Illinois

9:45 a.m.—*Management of Carbon Monoxide Intoxication*
Joseph F. Tomashefski, Earl T. Carter, Kenneth Coburn, Ph.D., and Fred Thelde, M.A., Columbus, Ohio

10:00 a.m.—*Resuscitation, Asphyxia and Cardiac Standstill*
Max Sadove, Chicago, Illinois

10:15 a.m.—*Monoamine Oxidase Inhibitors in the Treatment of Angina Pectoris*
Seymour L. Cole, Beverly Hills, California

10:30 a.m.—*Treatment of Occlusive Vascular Disease with Ethylenediaminetraacetic Acid (EATA)*
Norman E. Clarke, Detroit, Michigan

10:40 a.m.—*When and How to Use Quinidine for the Treatment of Cardiac Arrhythmias*
Samuel A. Weisman, Los Angeles, California

10:50 a.m.—*Histoplasmosis*
Michael L. Furcolow, Kansas City, Kansas

11:00 a.m.—*North American Blastomycosis of the Nasal Sinus*
Alvis E. Greer, Houston, Texas

11:10 a.m.—*Adjournment*

Saturday, October 17, Continued

8:55 a.m.—Scientific Session No. 6, Sandia Room

PRACTICAL CONSIDERATIONS OF CARDIOVASCULAR PHYSIOLOGY: APPLICATIONS IN MEDICINE AND SURGERY

Chairman:
Albert L. Maisel, Albuquerque, New Mexico

9:00 a.m.—*Hyperkinetic Cardiovascular Syndromes*
John Huston, Milwaukee, Wisconsin

9:15 a.m.—*Cardiovascular Dynamics*
E. E. Eddleman, Jr., Birmingham, Alabama

9:30 a.m.—*Coronary Blood Flow*
George G. Rowe, G. M. Maxwell, C. A. Castillo, and C. W. Crumpton, Madison, Wisconsin

9:45 a.m.—*Rare Congenital Malformations of the Heart with Correlation of the Clinical and Physiologic Features*
Benjamin M. Gasul, Chicago, Illinois

10:00 a.m.—*Hypertension*
John H. Moyer and Albert N. Brest, Philadelphia, Pennsylvania

10:15 a.m.—*Prevention of Arteriosclerosis in Young Men Filling Exacting Positions*
George C. Griffith, Los Angeles, California

10:30 a.m.—*Pathophysiology of Acute and Chronic Pericarditis*
William S. Blakemore, Philadelphia, Pennsylvania

10:45 a.m.—*RECESS TO VISIT EXHIBITS*

THE BODY COUNTER: DEVELOPMENT AND DIAGNOSTIC TECHNIC

11:00 a.m.—*Description of the Body Counter*
Wright H. Langham, Ph.D., Los Alamos, New Mexico

11:35 a.m.—*Clinical Applications of the Body Counter*
Clarence C. Lushbaugh, Los Alamos, New Mexico

12:05 p.m.—*Adjournment*

12:30 p.m.—ROUND TABLE LUNCHEON MEETINGS

C-1 ***"Preventive Surgery—Preventive Medicine" in the Management of Pulmonary Disease: Thickened Pleura; Atelectasis, Displaced Mediastinum; Cystic Disease***
Edgar W. Davis, Washington, D.C., *Moderator*
J. Maxwell Chamberlain, New York, New York
Marvin S. Harris, Los Angeles, California
Justin J. Wolfson, Albuquerque, New Mexico

C-2 ***The Use of Anticoagulants in Diseases of the Heart and Lungs***
John F. Briggs, St. Paul, Minnesota, *Moderator*
Alan Frankel, Albuquerque, New Mexico
George R. Herrmann, Galveston, Texas
Alexander Libow, Miami Beach, Florida

C-3 ***Minimal and Maximal Pulmonary Function Determinations***
Edwin R. Levine, Chicago, Illinois, *Moderator*
Albert H. Andrews, Chicago, Illinois
David P. Cardus, Albuquerque, New Mexico
A. N. Longfield, Albuquerque, New Mexico

MOTION PICTURE PROGRAM

A PROGRAM OF FILMS ON DISEASES OF THE CHEST WILL BE SHOWN CONCURRENTLY WITH THE SCIENTIFIC PROGRAM ON THURSDAY, FRIDAY AND SATURDAY, OCTOBER 15-17, FROM 9:00 A.M. TO 12:00 NOON

HOTEL RESERVATIONS—HOMECOMING MEETING

A reservation form for hotel accommodations in Albuquerque during the Silver Anniversary Homecoming Meeting of the College, October 14-17, 1959, may be found on page xxx of this issue of the journal. Members who plan to attend the Homecoming Meeting are urged to complete this form and mail it directly to the Western Skies Hotel, Albuquerque, New Mexico, at the earliest possible date.

SPECIAL EVENTS PROGRAM

Wednesday, October 14

8:00 p.m.—OPENING SESSION, Sandia Room

Thursday, October 15

3:00 p.m.—SPECIAL WEAPONS OF THE FUTURE, Kirtland Air Force Base*
7:00 p.m.—ENCHANTORAMA, Patio
Including chuck wagon supper and square dancing

Friday, October 16

7:00 p.m.—FIESTA NIGHT, Old Albuquerque*

Saturday, October 17

3:30 p.m.—SHORT TOURS, Indian, Spanish and Western Tours*
7:00 p.m.—COCKTAIL PARTY, Patio
8:00 p.m.—BANQUET, Main Ballroom
10:00 p.m.—DANCING, Main Ballroom

Sunday, October 18

9:00 a.m.—ALL-DAY TOURS, Santa Fe, Taos, Acoma (The Sky City)*
Please complete order form at end of program for reservations at above functions.

LADIES ACTIVITIES

Wednesday, October 14

10:00 a.m.—REGISTRATION, East Lobby
8:00 p.m.—OPENING SESSION, Sandia Room
9:00 p.m.—ENTERTAINMENT, Patio

Thursday, October 15

8:30 a.m.—HOSPITALITY ROOM, Room 242 (open until 1:00 p.m.)
9:00 a.m.—TOUR OF UNIQUE NEW MEXICAN HOMES, Albuquerque*
3:00 p.m.—SPECIAL WEAPONS OF THE FUTURE, Kirtland Air Force Base*
7:00 p.m.—ENCHANTORAMA, Patio
Including chuck wagon supper and square dancing

Friday, October 16

8:30 a.m.—HOSPITALITY ROOM, Room 242 (open until 12:00 noon)
12:30 p.m.—LUNCHEON, Four Hills Country Club*
Luncheon will be followed by "Color and Fashions of the Southwest," featuring fiesta dress originals, Indian jewelry and Southwestern folklore.
7:00 p.m.—FIESTA NIGHT, Old Albuquerque*

Saturday, October 17

8:30 a.m.—HOSPITALITY ROOM, Room 242 (open until 1:00 p.m.)
Brunch by the poolside. Shopping tours arranged.
3:00 p.m.—SHORT TOURS, Indian, Spanish and Western Tours*
7:00 p.m.—COCKTAIL PARTY, Patio
8:00 p.m.—BANQUET, Main Ballroom
10:00 p.m.—DANCING, Main Ballroom

Sunday, October 18

9:00 a.m.—ALL-DAY TOURS, Santa Fe, Taos, Acoma (The Sky City)*
Please complete order form at end of program for reservations at above functions.
Children's activities will include horseback riding, shuffleboard, swimming and tennis.

***All activities to be held at the Western Skies Hotel except those starred.**

Silver Anniversary Homecoming Meeting

Advance Registration

By completing this form and returning it at once to the Executive Offices of the College, you will avoid having to stand in line at the Registration Desk of the Homecoming Meeting in Albuquerque. Your badge and program, as well as luncheon, banquet, social events and tour tickets will be prepared in advance and will be awaiting your arrival at the Western Skies Hotel. Please complete both sides of this Advance Registration Form and mail promptly.

Kindly make checks payable to **Homecoming Meeting, American College of Chest Physicians.**

Return form to: American College of Chest Physicians
112 East Chestnut Street
Chicago 11, Illinois

THERE IS NO REGISTRATION FEE
ALL PHYSICIANS ARE CORDIALLY INVITED TO ATTEND

Advance Registration Form

Member..... Non-member.....

Please Print

Name .....

Address .....

City and State .....

Accompanied by .....

Hotel or Motel .....

Arrival Date..... Departure Date.....

Participant in program .....

I am enclosing my check in the amount of $..... for reservations as indicated on the reverse side of this form.

RESERVATION FORM

Special Events

Please indicate on the coupon below the number of tickets you will require for the special events, including the Enchantorama, Fiesta Night in Old Albuquerque, the Homecoming Banquet and the ladies' activities.

Tours

Three short tours have been planned for Saturday, October 17, from 3:00 p.m. to 5:00 p.m. Please select one of the tours, as listed on the coupon, and indicate the number of tickets required.

On Sunday, October 18, three all-day tours starting at 9:00 a.m. have been planned. They are as follows:

Taos—Taos Indian Pueblo, Kit Carson House, Art Colony, Mission Ranchos de Taos.

Santa Fe—Oldest capital in the United States, Palace of the Governors, State Art Museum, Oldest Church, Laboratory of Anthropology, International Museum of Folk Art; also Santo Domingo Indian Pueblo.

Acoma (the Sky City)—Laguna Indian Pueblo and Uranium Mill.
Lunch is extra for all-day tours.

Two to three day tours to Mexico, Mesa Verde in Colorado, Grand Canyon in Arizona, and Las Vegas, Nevada, will be arranged through Globetrotters Travel Agency, 2212 Central, S.E., Albuquerque, New Mexico. Costs will be at their regular rates.

Please make checks payable to **Homecoming Meeting, American College of Chest Physicians.** Checks must accompany all requests for reservations and will be accepted in the order in which they are received. All tickets will be held for pick-up at the College Registration Desk, Western Skies Hotel.

Round Table Luncheons—**Tickets: $3.50 each**

	Thurs., Oct. 15	Fri., Oct. 16	Sat., Oct. 17
First Choice	A.....	B.....	C.....
Second Choice	A.....	B.....	C.....
Third Choice	A.....	B.....	C.....

Please indicate choice by number as listed in program

Special Events		No. of tickets
Enchantorama, Thursday October 15,	**$5.00 each**	.....
Fiesta Night, Friday, October 16,	**$5.00 each**	.....
Homecoming Banquet, Saturday, October 17, (including cocktails, dinner, dancing)	**$9.50 each**	.....

Ladies Activities		
Ladies Tour, Thursday, October 15,	**$1.00 each**	.....
Ladies Luncheon, Friday, October 16,	**$4.50 each**	.....

Tours

Short Tours (2 hours), Saturday, October 17, **$1.50 each**
Check one:

.....Indian Pueblo .....Spanish Settlement .....Western Ranch

No. of tickets .....

All-day Tours, Sunday, October 18, **$5.00 each**
Check one:

.....Taos .....Santa Fe .....Acoma

No. of tickets .....

new in the chemotherapy of tuberculosis

Pheny-PAS-Tebamin

TABLETS CHOCOLATE FLAVORED POWDER

Brand of Phenyl p-Aminosalicylate U.S. Patent No. 2650483

a new effective PAS derivative

distinguished by its freedom from gastrointestinal irritation

71.7 per cent BETTER TOLERATED than K PAS[1]

53.4 per cent BETTER TOLERATED than Ca PAS[1]

49.9 per cent BETTER TOLERATED than Na PAS[1]

30.7 per cent BETTER TOLERATED than the anionic exchange resin of PAS[1]

PAS, in all forms available to date, is definitely irritating to the gastrointestinal tract. 'Pheny-PAS-Tebamin' however, because it (1) is nonirritating in itself and (2) is not hydrolyzed to free irritating PAS until after absorption, possesses all the chemotherapeutic properties of PAS but does not behave like PAS in the gastrointestinal tract. 'Pheny-PAS-Tebamin' was well tolerated in 86 per cent of 242 patients receiving as much as 24 Gm. orally per day for periods up to 10 months.[1-5]

RECOMMENDED DOSAGE: Tablets: Eight (8) tablets taken with water, fruit juice or milk three times daily at mealtime or as prescribed by physician. Powder: One level tablespoonful of chocolate flavored powder suspended in water or milk three times daily at mealtime or as prescribed by physician.

SUPPLY: Tablets in bottles of 500, 5,000 and 25,000. Each tablet contains 0.5 Gm. 'Pheny-PAS-Tebamin'. Powder in canisters of 1, 5 and 25 lbs. Each tablespoonful (8 Gm.) of powder contains 4 Gm. 'Pheny-PAS-Tebamin'.

CITED REFERENCES: 1. Cohen, S. S., Yue, W. Y., Tsai, S. H.: Antibiotics Annual, 1958-1959, New York, 1959 pp. 121-124. 2. Meyer, H. C.: Antibiotics Annual, 1957-1958, New York, 1958 pp. 614-618. 3. Berger, G., Langer, W.: Wien. med. Wchnschr. 108:570 (July 5) 1958. 4. Törning, K., Jensen, K. A., Kiner, I.: Personal Communication. 5. Balogh, A., Suess, H. O.: Wien. med. Wchnschr. 108:499 (June 14) 1958.

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